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Journal of the AMERICAN MEDICAL WOMEN'S ASSOCIATION

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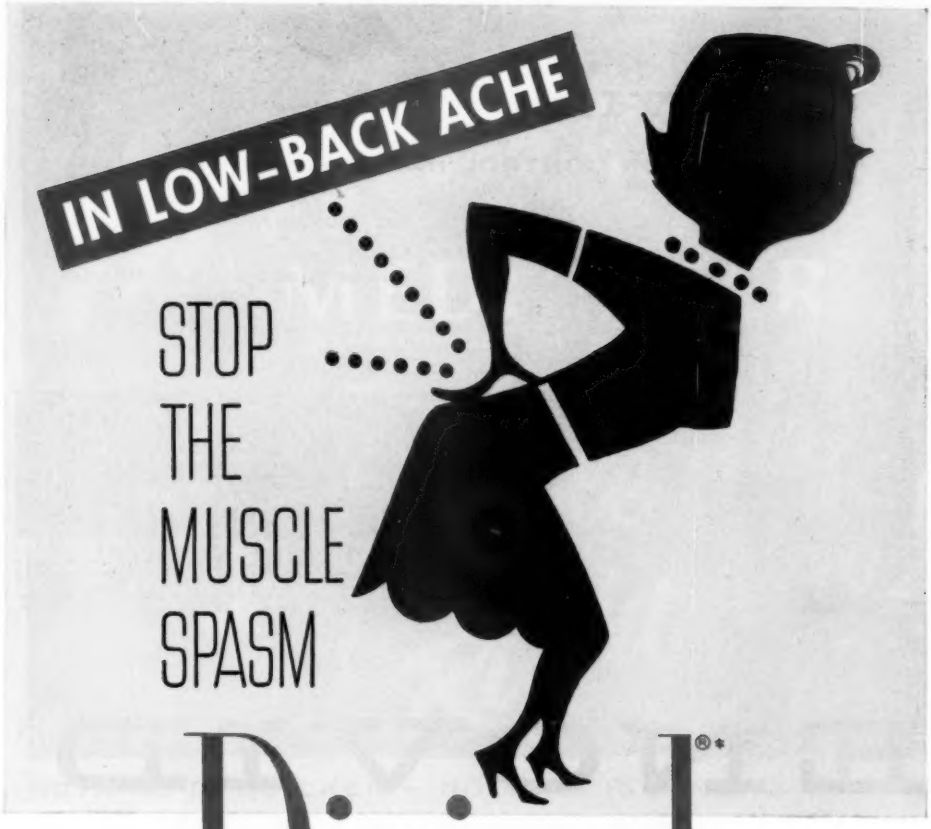

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Volume 13 | FEBRUARY, 1958 | Number 2

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Tolbutamide (Orinase) in the Treatment of the Ambulatory Patient with Diabetes Mellitus, *Roy C. Gumpel, M.D., Alexander G. Vongries, M.D.,* and *Elaine P. Ralli, M.D.* 39

Observations on Training for Childbirth, *Lawrence Zelic Freedman, M.D.,* and *Herbert Thoms, M.D.* 46

Some Effects of Mineral Elements in Nutrition, *Thomas H. Jukes, Ph.D.* 52

The Female Patient Who Works, *Beatrice Mintz, M.D., M.P.H.* 58

Arachnodactyly (Marfan's Syndrome): Case Report, *Jean Crump, M.D., F.A.A.P., Rose M. Mikelberg, M.D.,* and *Elizabeth M. S. Recknagel, M.D.* 62

SPECIAL FEATURES

New Honor for Helen Johnston, M.D. 71

MWIA 1958 International Tour 72

REGULAR FEATURES

Medical Highlights 67

President's Message 70

Opportunities for Women in Medicine 74

These Were the First, ELIZABETH BASS COLLECTION 76

News of Women in Medicine 77

Book Notices 78

MISCELLANEOUS

Editorial Board ..... Adv. p. 6

Board of Directors ..... Adv. p. 9

Branch Officers ..... Adv. p. 14

Junior Branch Officers ..... Adv. p. 32

Index to Advertisers and Products Advertised ..... Adv. p. 36

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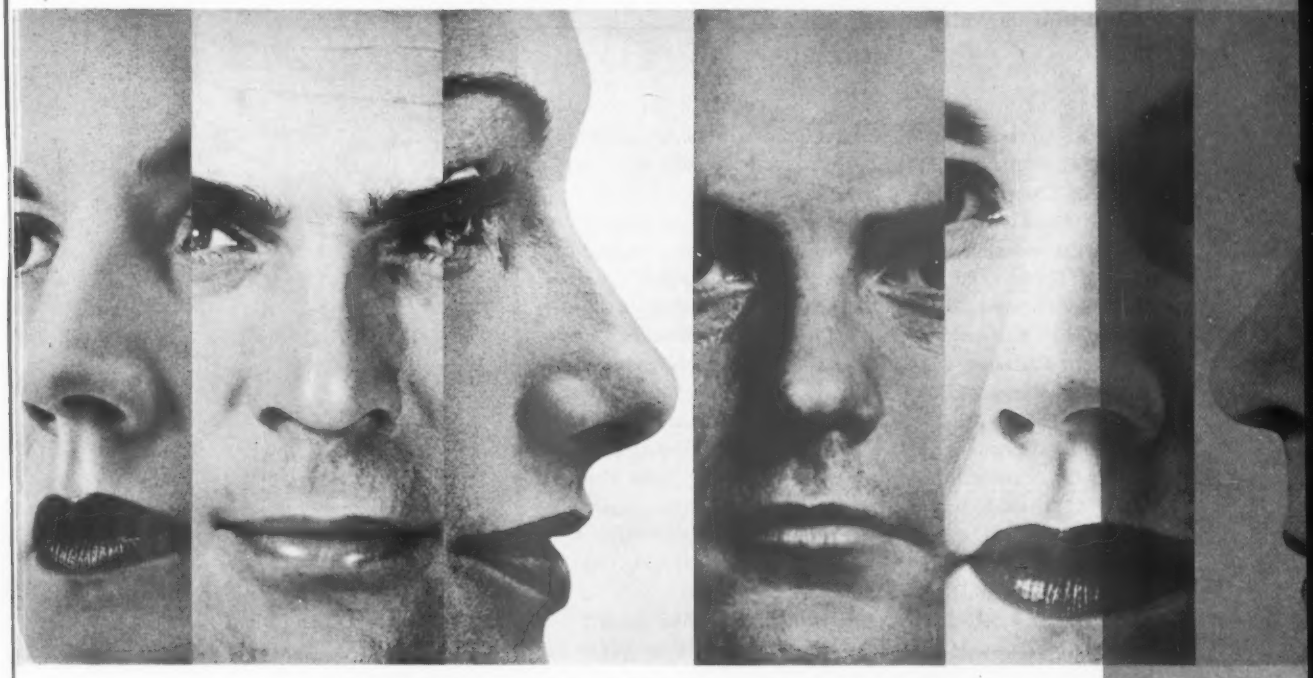

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(Continued on page 16)

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(Continued on page 19)

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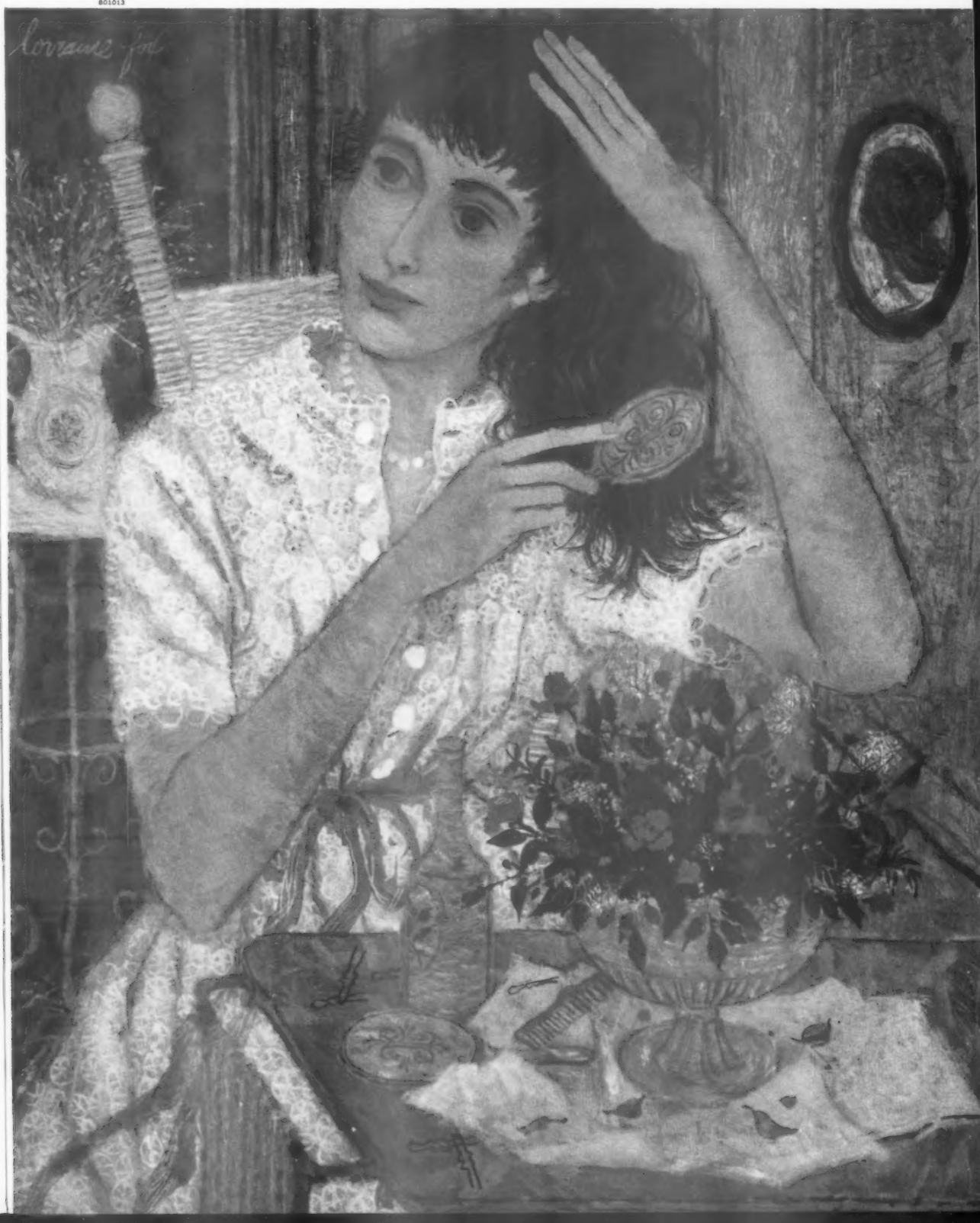

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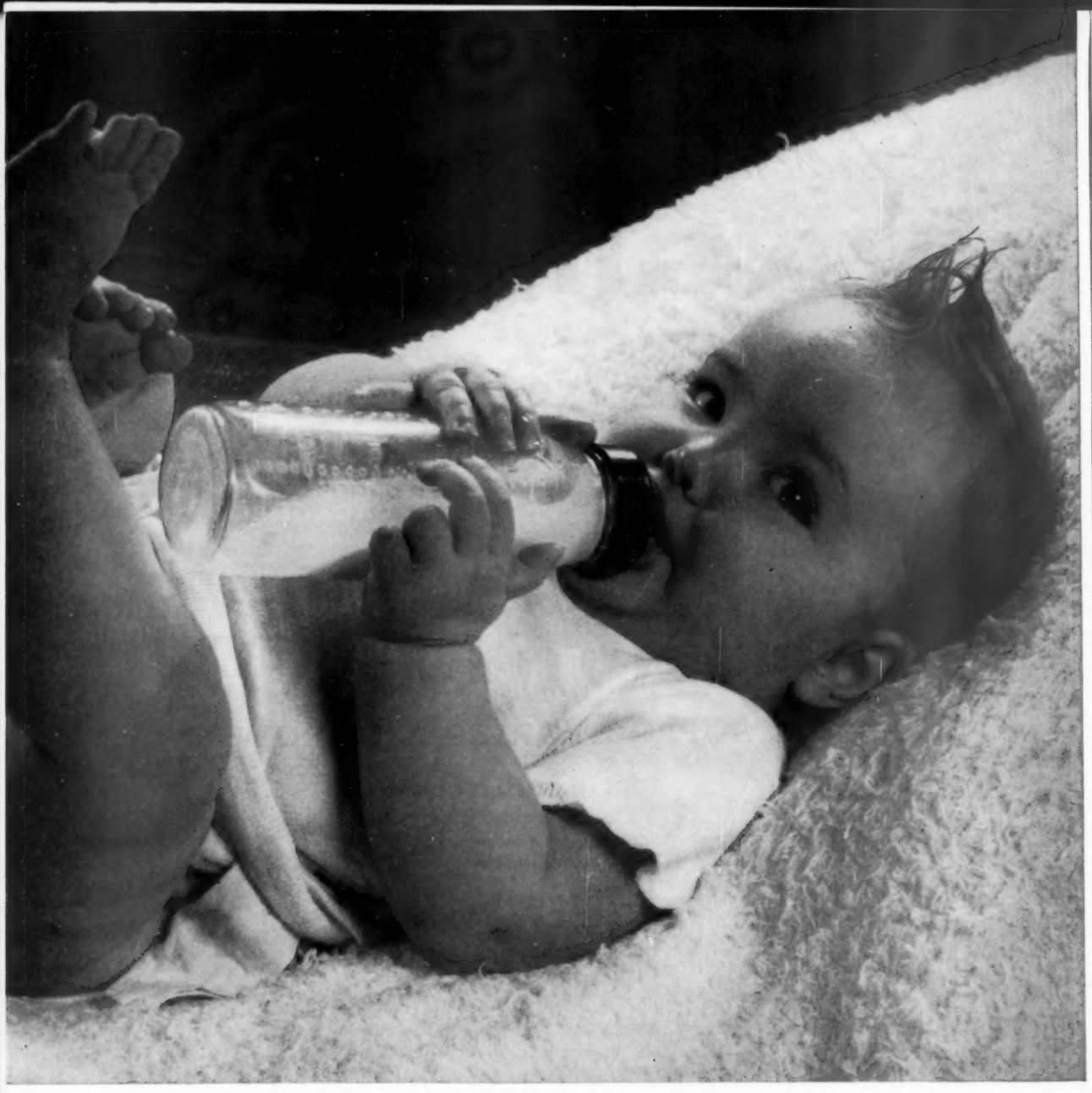

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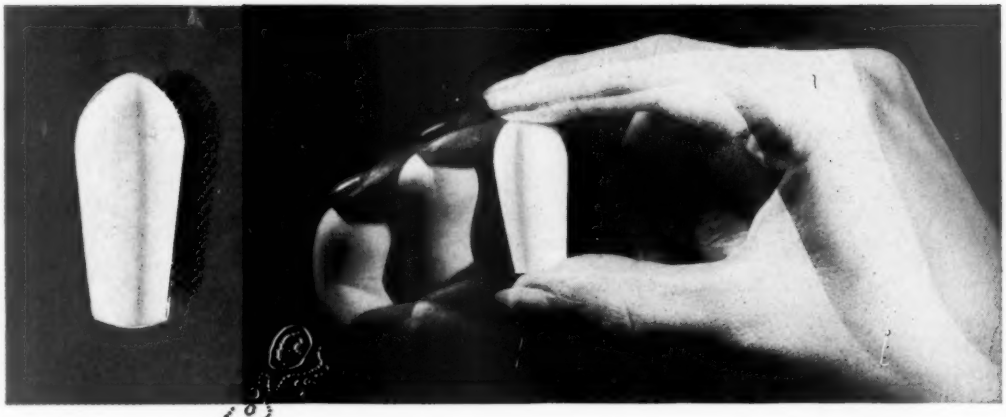

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a balanced eating plan[1,2,3]

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1. *Eisfelder, H.W.: Am Pract. & Dig. Treat. 5:778 (Oct. 1954)*
2. *Freed, S.C.: G.P. 7:63 (1953)*
3. *Sherman, R.J.: Medical Times, 82:107 (Feb. 1954)*

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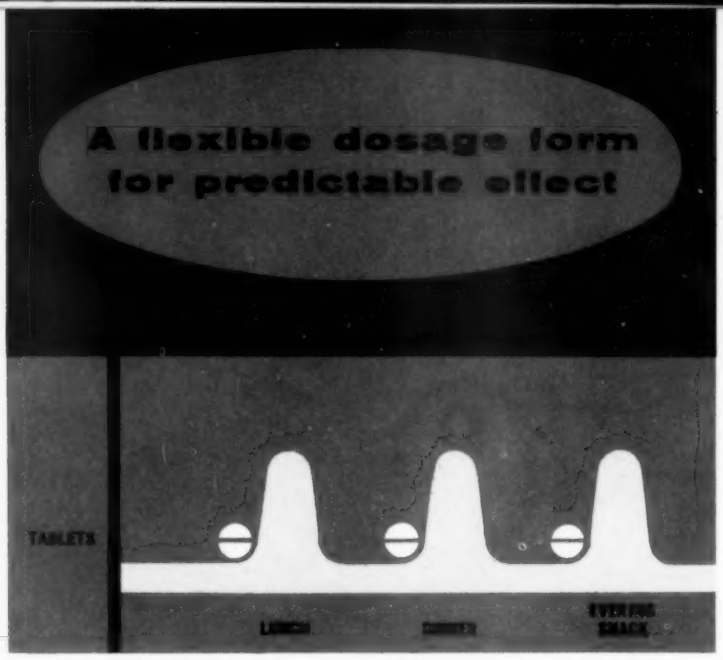

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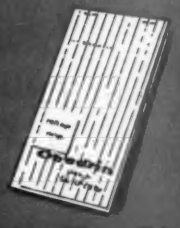

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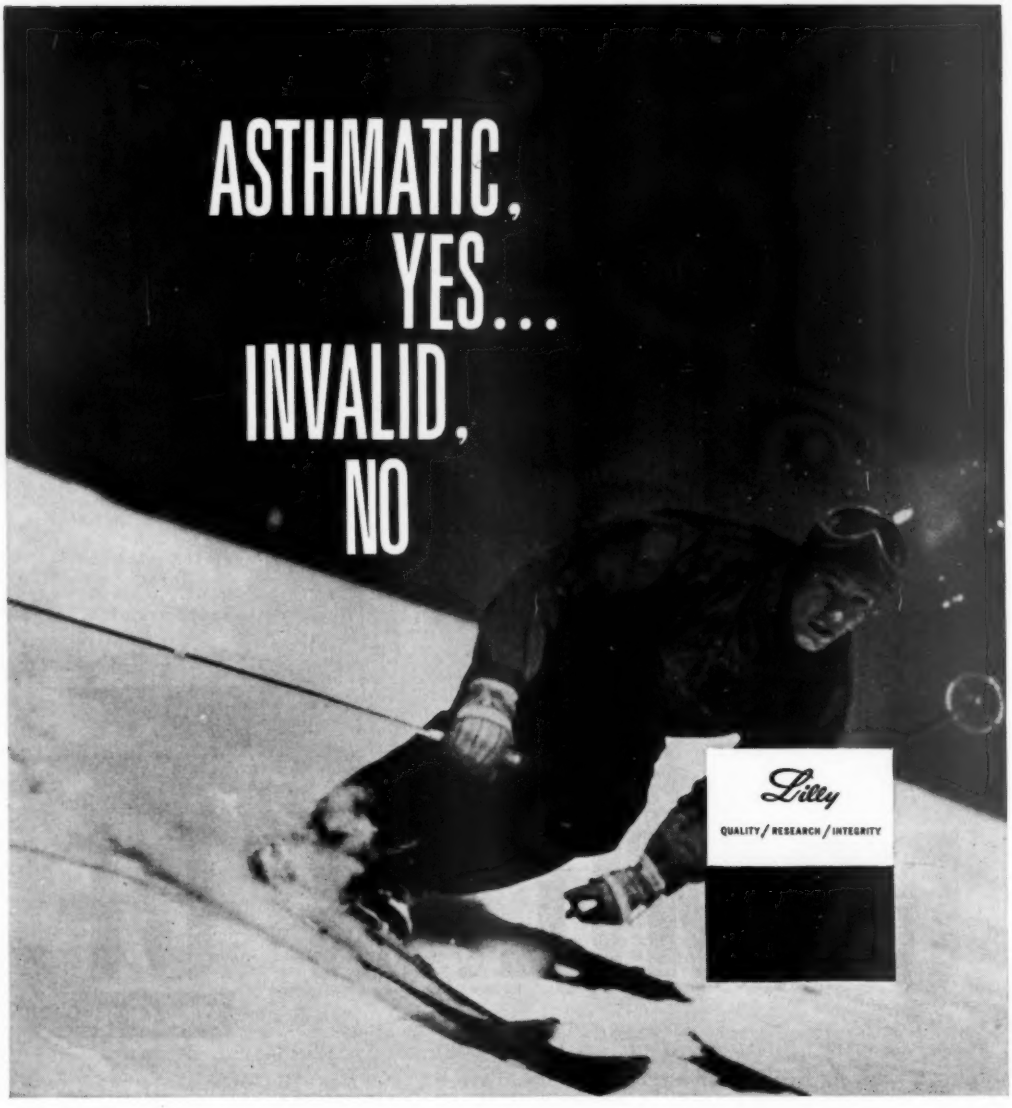

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Journal of the
AMERICAN MEDICAL WOMEN'S ASSOCIATION

Volume 13 FEBRUARY, 1958 Number 2

Tolbutamide (Orinase) in the Treatment of the Ambulatory Patient with Diabetes Mellitus*

Roy C. Gumpel, M.D., Alexander G. Vongries, M.D., and Elaine P. Ralli, M.D.

THIS REPORT IS CONCERNED with the effects of tolbutamide (Orinase) on a group of ambulatory diabetic patients who received therapy with the drug for 4 to 20 months. The patients had been regularly attending the clinics for much longer periods, so that the period of observation was never less than six months and in the majority of cases extended over many years. During the period of tolbutamide therapy the patients visited the clinic three times a week at the onset of therapy and every two weeks once the maintenance dose of tolbutamide was well established. The patients attended the Diabetic Clinics of the Third (New York University) Medical Division of Bellevue Hospital and the Diabetic Clinics of the Lenox Hill Hospital.

*This work was supported by grants from The Upjohn Company and The Diabetes Study Group of New York University-Bellevue Medical Center.

In view of the observation [1,2] that tolbutamide is not effective in the adolescent or young diabetic patient, most patients selected for treatment were the ones who had developed diabetes after the age of 40 years. However, we did attempt therapy in some patients who had developed diabetes at an earlier age.

METHOD OF THERAPY

In patients who were receiving small doses of insulin (10 or 15 units), insulin was usually discontinued entirely before tolbutamide was administered. During this period blood sugar determinations were taken once or twice a week to establish the blood sugar range while the patient was not receiving insulin. In many of the cases this period was quite long, as is shown in table I. Some patients who were receiving only small doses of insulin were able to remain fairly well controlled without any insulin for much longer periods

Dr. Gumpel is U.S. Public Health Service Trainee Fellow.
Dr. Vongries is Assistant Attending Physician, Lenox Hill Hospital, New York City.
Dr. Ralli is Visiting Physician, Bellevue Hospital, and Assistant Professor of Medicine, New York University-Bellevue Medical Center.

TABLE I

Patients Successfully Treated with Tolbutamide

Group	Case No.	Sex	Age at Onset of Diabetes, Yr.	Duration of Diabetes, Yr.	Insulin Data			Blood Sugar Range Prior to Tolbutamide Therapy (No Insulin)		Tolbutamide Therapy Period (No Insulin)		
					Years on Insulin	Units	Blood Sugar Range, Mg./100 cc.	Period, Wk.	Blood Sugar Range, Mg./100 cc.	Duration of Therapy, Mo.	Gm. Daily	Blood Sugar Range, Mg./100 cc.
A. Patients who had not received insulin or who only required it at intermittent intervals	1	F	57	4	—	—	—	2	267-339	20	3-2	113-269
	29	M	50	7	—	—	—	36	165-330	9	2	117-167
	30	F	56	1	—	—	—	4	190-204	8	3-1.5	94-228
	85	F	34	23	20	(intermittently)	—	3	206-174	4	2	145-177
	34	F	49	2	—	—	—	4	282-363	7	4.5-3	151-196
	86	F	64	14	10	(intermittently)	—	1	250-326	4	2	103-149
	37*	F	71	5	—	—	—	3	146-158†	4	3	111-129
	40	M	58	2	—	—	—	1	190-264	6	1-0.5	80-132
	69‡	M	41	25	—	—	—	3 yr.	100-275	7	3-2	140-210
	70	F	67	1	—	—	—	5	120-179	6	2-3.5	105-137
	71	F	45	2	—	—	—	60	115-260	12	0.5-2	80-142
	84	F	58	2	—	—	—	2	264-267	6	3-2	111-298
B. Patients requiring insulin. Insulin was stopped for varying periods before initiating therapy with tolbutamide	3	M	63	3	10 mo.	20	139-176	4	156-232	20	2	92-197
	5	F	51	3	3	25	149-268	1	268-	15	3-2	147-214
	6	M	48	14	1	25	150-202	1	196-	15	3-1.5	107-148
	7	M	42	1	1	10	114-182	10	145-228	14	1.5-1	81-204
	8§	F	48	8	8	25	60-230	1	200-	11	4-1.5	80-210
	9	F	61	14 mo.	9 mo.	20	85-140	8	101-170	13	3-0.5	90-150
	18	F	62	2	1	25	165-265	1	218-	11	3-1.5	91-155
	10	F	66	11	11	15	324	1	302-349	13	3-1.5	103-208
	11	F	59	11	6 mo.	12	140-159	14	105-487	13	3-1.5	72-263
	12	M	58	14	2	15	179-208	2	284-322	13	3-1.5	93-209
	13	F	41	20	2	15	—	3	204-244	14	2-1	108-182
	14	M	38	2	2	15	150-184†	26	130-185	12	3-0.5	99-154
	15	F	64	2	2	30	—	14	120-250	14	3-2	106-185
	16‖	M	67	1	5 mo.	25	165-263	2	190-259	7	3-1	83-170
	17	F	65	1	1	40	210-256	1	231-	12	2	109-171
	20	F	55	4 mo.	4 mo.	15	89-214	8	152-333	12	4.5-2	101-274
	21	F	52	9	9	30	—	2	267-277	13	2	95-212
	23	M	59	7	2 (irr.)	10	125-185	?	?	12	1	112-132
	24	M	51	15	6	25	159-222	5	182-246	10	2	111-176
	25	M	55	4	2	20	—	3	186-231	10	3-1	86-152
	22	M	49	1	1	15	153-251	—	—	12	3	138-231
	26	F	57	2	2	30	150-215	3	155-175	9	3-1	85-150
	36	M	53	13	4	12	117-267†	10	231-264	6	3	157-192
	39	M	59	10	4	10	90-230	1	230-	6	3-1	80-145
	32	F	60	3 mo.	1 mo.	40	275†	2	200-340	8	2	132-270
C. Patients receiving insulin during initiation of tolbutamide therapy	2	M	66	2	1	15	160-237	—	—¶	19	3-2	113-231
	4	F	48	8	2	25	150-250	—	—¶	17	3-2	127-208
	19	M	56	2	2	20	233-308	—	—¶	11	3-4	110-252
	27	M	67	2	2	20	212-274	—	—¶	6	2	115-247
	28	F	52	18	17	20	174-242	—	—¶	8	3-2	106-218
	33	F	32	3	1	18	206-433	—	—¶	6	3	90-114
	66	M	61	3	3	20	197-205	—	—¶	6	2-3	104-175

*Died of intestinal obstruction.
†Fasting blood sugars.
‡This patient only received insulin for a short time during an infection.
§This patient did well on tolbutamide for 11 months. The blood sugar level then rose to above 200 mg. per 100 cc. and remained elevated and glycosuria appeared. Tolbutamide therapy was discontinued and patient returned to 15 units of insulin daily, with a prompt fall in the blood sugar level.
‖Tolbutamide therapy was interrupted after two months because of a rash. Started again seven months later and continued for five months. Rash appeared again and drug therapy was again stopped.
¶These patients were given decreasing doses of insulin during initiation of tolbutamide therapy—a period of one to two weeks. Use of insulin was then discontinued.

than we had anticipated. One patient, for example, did not require any insulin for six months, and it was only in the later part of that period that the blood sugar level became significantly elevated. In patients who had required larger doses of insulin, we decreased the insulin dosage while observing the blood sugar levels and, with the insulin decreased, began tolbutamide therapy, discontinuing insulin gradually during the first week or so of therapy.

Patients were started on therapy with 1 Gm. of tolbutamide three times a day. When the blood sugar level was satisfactorily controlled, the dose was reduced to 2 Gm. daily and, if the diabetes was well controlled on this dose, tolbutamide was further reduced to 1 Gm. a day. In several instances, the diabetes was well controlled on only 0.5 Gm. a day.

Blood Sugar Determinations. In view of the fact that all of the patients were ambulatory, we felt that it was more reasonable to take the blood samples at a specified time after breakfast rather than after fasting. Therefore, blood sugar tests were done two hours after the breakfast meal. The patients were given a record sheet on which they kept a report of the daily urine tests. Most of them were reliable about keeping these records, thus providing us with an additional index on whether the diabetes was controlled. The urine was tested four times a day using Clinitest tablets.

Intravenous Tolbutamide Test. In 28 patients we used the intravenous tolbutamide test described by Sherry.[3] In this test the blood sugar levels are determined before and two hours after the intravenous administration of 1 Gm. of the drug. The percentage decrease in blood sugar is an indication as to whether or not the patient will respond well to therapy.

RESULTS

A total of 69 patients have been followed for periods of 4 to 20 months. The majority have been observed for at least one year. Forty-four of this group were successfully treated with an average daily dose of 1.5 Gm. of tolbutamide. One patient became resistant to therapy after 11 months (case no. 8).

Results in successfully treated patients are shown in table I, which is divided into three parts: patients (group A) who had never required insulin but whose blood sugar levels were well above normal limits; patients (group B) who had been receiving insulin, in whom insulin therapy was stopped prior to the initiation of tolbutamide therapy (the group of patients in whom we did not initiate tolbutamide therapy until the blood sugar level indicated that there was need for therapy other than diet); and patients (group C) who had been receiving insulin, in whom insulin therapy was continued during the adjustment period with tolbutamide.

The youngest patient in the successfully treated group (table I) was 32 and the oldest 71 years; the average age was 55 years. Diabetes in these patients had been present from three months to 25 years, and in 12 patients diabetes was present for more than 10 years. Thirty-two of the patients had required insulin daily and duration of insulin therapy was from one month to 17 years. Two patients (cases 85 and 86) had taken insulin intermittently for short periods of time.

The amounts of insulin taken by the patients varied from 10 to 40 units daily. Only 2 required as much as 40 units daily (cases 32 and 17), but 20 patients were taking 20 or more units daily. Possibly the patients taking 40 units of insulin actually did not require this much insulin to control their diabetes. In both these cases, insulin therapy was discontinued only for one and two weeks prior to starting tolbutamide therapy. In both instances the control of diabetes with tolbutamide, as judged by the urine tests and the blood sugar determinations, was prompt and satisfactory. In only 1 patient (case 8) in the group reported in table I has the course of diabetes required a return to insulin. This female patient developed diabetes at the age of 48 years, had required 15 to 25 units of insulin daily, and had the disease for eight years at the time she was started on tolbutamide therapy. After use of insulin was discontinued for one week, sugar appeared in the urine, and the blood sugar level rose to 200 mg. per 100 cc.; at this point, tolbutamide therapy was started. She was well controlled on tolbutamide for 11 months; then she began to spill sugar and her blood sugar level again rose to over 200 mg. per 100 cc. During part of this time she had a mild respiratory infection that may well have increased the severity of her diabetes, but even when this was controlled the blood sugar level did not respond to tolbutamide, even though the dose was increased to 6 Gm. daily. Therapy with the drug was therefore discontinued, and she is now receiving 15 units of insulin a day.

¶These patients were given decreasing doses of insulin during initiation of tolbutamide therapy—a period of one to two weeks. Use of insulin was then discontinued.

TABLE II

Patients Who Did Not Respond to Tolbutamide Therapy

Group	Case No.	Sex	Age at Onset of Diabetes, Yr.	Duration of Diabetes, Yr.	Insulin Data			Blood Sugar Range Prior to Tolbutamide Therapy (No Insulin)		Period of Transition While Receiving Both Insulin and Tolbutamide				Orinase Therapy Period (No Insulin)		
					Years on Insulin	Units	Blood Sugar Range, Mg./100 cc.	Period, Wk.	Blood Sugar Range, Mg./100 cc.	Period, Wk.	Insulin, Units	Orinase, Gm.	Blood Sugar Range, Mg./100 cc.	Duration of Therapy, Wk.	Gm. Daily	Blood Sugar Range, Mg./100 cc.
A. Patients who had never received insulin therapy.	44	M	55	12	—	—	—	2	238-278	—	—	—	—	2	3-4.5	210-275
	51	M	51	13	—	—	—	2	337-372	—	—	—	—	3	2-4	297-394
	55	F	58	2	—	—	—	—	300	—	—	—	—	32	3	112-314
	57	F	65	>1	—	—	—	12	368-451	—	—	—	—	36	2-4	161-315
	58	F	49	3	—	—	—	2	297-387	—	—	—	—	3	3	360-367
	60	F	60	5	—	—	—	1	270-354	—	—	—	—	4	3	244-303
	73	F	60	13	—	—	—	3	238-248	—	—	—	—	7	2-3	160-238
B. Patients requiring insulin, in whom insulin therapy was stopped prior to tolbutamide therapy	48	F	64	3	>1	15	—	2	139-222	—	—	—	—	28	3-6	129-237
	50	F	55	19	19	15	—	1	244-331	—	—	—	—	2	2-3	211-248
	43	M	51	6	2	15	—	14	215-263	—	—	—	—	4	3	194-228
C. Patients in whom use of insulin was continued during the adjustment period with tolbutamide	27	M	62	2	2	20	142-274	—	—	1	10	2	160	13	2	202-147*
	45	M	43	31	31	40	128-319	—	—	5	30-40	3	222-263	—	—	—
	46	F	64	6	6	15	347-351	—	—	1	15	3	333	2	3	281-375
	47	F	54	9	>1	35	222-324	—	—	8	25	3-4.5	250-300	—	—	—
	49	F	37	2	2	15	150-289	—	—	1	5	2	246	11	3-4	177-336
	52	F	61	3	3	15	331-470	—	—	5	30	3-4.5	252-351	—	—	—
	53	F	69	>1	>1	25	248-285	—	—	4	10-5	3	177-230	9	3-4.5	191-240
	54	M	33	23	23	70	160-196	—	—	1	70	3	225-338	—	—	—
	56	F	36	22	22	30	—	—	—	7	20	3	167-357	—	—	—
	59	M	51	18	18	20	189-282	—	—	1	10	3-4.5	238-248	—	—	—
	61	M	9	9	9	40	275-438	—	—	4	20-40	2-3	298-369	—	—	—
	62	F	60	10	8	25	255-264	—	—	6	15	2-3	246-279	—	—	—
	63	F	64	4	4	55	212-344	—	—	2	20-45	2-4	294-301	—	—	—
	68	F	41	18	18	40	230-337	—	—	5	10	3	186-314	—	—	—
	64	F	30	15	15	25	134-246	—	—	8	10	3	281-165	—	—	—

*Allergic to drug.

In table II are the data on patients whose diabetes was not controlled by tolbutamide. Included are 5 diabetic patients who had developed the disease before the age of 40 years. Also included are 11 patients who had diabetes for 10 years or more; of these, 7 had the disease for 15 years or more. Although 7 of the patients in this group never had been treated with insulin, they all had very high blood sugar levels. Two were treated for periods of 32 to 36 weeks with tolbutamide, but it was unsuccessful and they had to be started on insulin therapy. In 3 patients (group B in table II) we discontinued insulin therapy prior to starting therapy with tolbutamide. These patients all had high blood sugar levels and none responded to tolbutamide therapy. Group C in table II includes 15 patients, all but 3 of whom were taking more than 15 units of insulin daily. We did not attempt to discontinue use of insulin prior to starting tolbutamide therapy in this group but decreased it during the period of transition. In this group only 3 patients were treated with tolbutamide alone because of the fact that, when they were receiving both tolbutamide and insulin, the blood sugar levels had remained high.

SIDE EFFECTS OF THE DRUG

Seven patients developed a skin rash, which was either maculopapular or erythematous and occasionally pruritic. In each case use of the drug was discontinued. Drug therapy was reinstituted later in some cases and the rash did not always reappear. In one instance, a patient developed angioneurotic edema, apparently due to allergy to the drug. We have not seen any instances of leukopenia or agranulocytosis.

We did observe that in the elderly diabetic patient there was apt to be a more rapid fall in the blood sugar level than we had anticipated. This was at times associated with symptoms of hypoglycemia.

Two patients required hospitalization during therapy (cases 37 and 44). One was an elderly Negro man who developed symptoms suggestive of hypoglycemia with the possibility of a coronary thrombosis. The electrocardiogram showed only minor abnormalities. This patient recovered, was placed on insulin, and is attending the clinic and doing well. The other patient was admitted to the hospital for intestinal obstruction and died after an operation. This patient's diabetes had been well controlled on the drug, and there was no reason to suggest that the death was in any way due to use of the drug.

In table III are recorded the results of the "Orinase Tolerance Test" in 28 patients. This test may serve as a guide to whether patients will respond successfully to therapy with tolbutamide. Obviously, it cannot be relied upon completely. Presumably, if the blood sugar level decreases 15 per cent or more, the patient will respond to tolbutamide therapy. Exceptions to this rule are indicated in the table, where it is shown that, in 6 patients in whom the blood sugar fall was 15 per cent or more, therapy was unsuccessful.

DISCUSSION

It appears from our experience and from that of other observers[4] that patients in whom diabetes existed for more than five years are not as liable to respond as are patients who have had the disease for a shorter period. However, in our group 12 of 44 patients who were successfully treated had the disease for more than 10 years. On the basis of our observations it seems fairly clear that tolbutamide is particularly useful in the patient who has not been on insulin therapy for more than five years, and who has developed diabetes at age 40 years or more. These criteria are now recognized by most observers and are a good guide to the type of patient to select for therapy. There are exceptions to these rules (table I), and treatment may be given to patients who have had diabetes for longer periods but in whom the disease has been mild and who have required only small amounts of insulin. The patients must be kept under careful observation during therapy.

In initiating therapy insulin may be discontinued if the dose has not been more than 15 units daily. If one is decreasing the dose of insulin at the same time that tolbutamide therapy is started, the insulin dose should be reduced approximately one-half and tolbutamide therapy started in doses of 2 to 3 Gm. daily. In the elderly diabetic patient, owing to the rather rapid fall in the blood sugar level occasionally observed, the initial dose of the drug can be 2 Gm. daily.

Our patients are carefully instructed to report any untoward signs immediately. They are seen in the clinic three or four times weekly during the first two weeks of therapy, then twice a week, then once a week, and then every two weeks. When patients have been

TABLE III

Orinase (Tolbutamide) Tolerance Test: Effects of Administering 1 Gm. of Tolbutamide Intravenously on the Percentage Decrease in the Blood Sugar Level After Two Hours

Case No.	Sex	Age at Onset, Yr.	Duration of Diabetes, Yr.	Insulin Therapy, Yr.	Daily Dose of Insulin, Units	Drop of Blood Glucose After Tolbutamide Therapy Intravenously, %	Outcome of Therapy with Tolbutamide
24	M	50	15	6	10-25	52	Successful
19	M	56	2	2	20	42	Successful
22	M	48	> 1	> 1	20	30	Successful
62	F	60	10	8	25	28	Unsuccessful
16	M	67	1	> 1	25	26	Successful
28	F	52	18	17	20	25	Successful
32	F	60	> 1	> 1	30	23	Successful
13	F	41	20	2	15	21	Successful
56	F	37	22	22	30	21	Unsuccessful
64	F	30	15	15	25	16	Successful
50	F	55	19	19	15	16	Unsuccessful
52	F	61	3	3	15	16	Unsuccessful
72	M	45	> 1	> 1	25	14	Unsuccessful
73	F	60	13	0	0	13	Unsuccessful
49	F	57	2	1	15	13	Unsuccessful
61	M	14	9	9	55	11	Unsuccessful
47	F	54	9	> 1	35	11	Unsuccessful
58	F	45	3	0	0	7	Unsuccessful
74	M	26	10	10	10	7	Rx not attempted
41	M	71	> 1	0	0	20	Successful
31	F	63	15	0	0	19	Successful
34	F	49	2	0	0	20	Successful
33	F	32	3	0	0	15	Successful
68	F	41	18	18	40	16	Unsuccessful
66	M	61	3	> 1	20	12	Successful
77	M	43	9	8	20	12	Successful
78	M	58	15	15	20	22	Successful
79	M	41	10	3	30	20	Unsuccessful

successfully treated with the drug for a period of a year, the interval between visits can be prolonged to two months or more. The patients should be warned that the drug is toxic and may produce a rash, and that if this occurs use of the drug should be discontinued and the patient should report to the clinic immediately.

The literature on tolbutamide is already quite voluminous, and excellent symposia reports have appeared.[5,6] However, the mechanism of the action of tolbutamide in reducing the blood sugar level is still a subject of some discussion. Tolbutamide is not a substitute for insulin in that it does not increase the glucose utilization of muscle in vitro in the absence of insulin.[7,8] Neither does it increase glucose utilization in the eviscerated rat.[9] Finally, it does not appear to lower the blood sugar level in the completely depancreatized dog.[10,11] At the present time, the effect of tolbutamide is best explained by its action on the beta cells of the islets of Langerhans, which are, following its administration, stimulated to liberate insulin, as demonstrated by the degranulation of the beta cells following tolbutamide therapy.[12,13] However, the possibility that tolbutamide may either sensitize the tissues to the effect of endogenous insulin or may overcome an insulin antagonist should not be overlooked, as either of these possibilities may explain its action.

Although it is possible that at certain times some of these patients would be well controlled on diet alone, it has seemed better to us to continue use of the drug at a low dosage schedule than to start and stop drug therapy. The drug provides an excellent means of keeping the blood sugar levels within normal limits. The smallest daily dose that controls the diabetes is the one that should be used. In certain cases, only 0.5 Gm. a day will be re-

quired. As far as we can ascertain, on the basis of the cases that we have followed now for 20 months, there has been no evidence of any serious side effects from the drug and the patients have felt well on the therapy.

SUMMARY

The effects of tolbutamide (Orinase) have been studied in 69 patients with diabetes mellitus who have been attending the Diabetic Clinics of the Third (New York University) Medical Division of Bellevue Hospital and of the Lenox Hill Hospital.

Of these 69 patients, 44 were successfully treated with tolbutamide and have now been observed for periods of from 4 to 21 months. Of the successfully treated group, 12 had not required insulin, except for 2 patients who had received insulin intermittently, prior to tolbutamide therapy. However, the blood sugar levels in these patients were well above the normal limits and were associated with considerable glycosuria. The other 32 patients had all required insulin and had been receiving insulin for from one month to 17 years. Only 2 of these patients had been on insulin therapy for more than 11 years. The majority of the patients had required from 10 to 30 units of insulin daily, and 2 patients had been on 40 units of insulin daily.

The dose of tolbutamide required to maintain the blood sugar level within normal limits in these 44 patients varied from 0.5 to 3 Gm. daily. The majority of the patients required 1.5 Gm. All but 3 had developed their diabetes over age 41 years. The average age of onset of the successfully treated group was 55 years.

The pertinent fact about the patients who did not respond to tolbutamide therapy was the duration of the diabetes. Half of the patients in this group had required more than 30 units of insulin daily to control the diabetes.

No serious side effects from the drug were noted. Although a rash occurred in 7 patients, none showed any abnormality in the number or character of the white blood cells.

Tolbutamide appears to provide a method of therapy that is useful in the older diabetic patient who has not been on insulin for more than 10 years and whose insulin requirement has not been excessive.

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Observations On Training for Childbirth

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IN ITS HISTORICAL DEVELOPMENT psychiatry has progressively pushed its area of awareness outward into the environment of its patients and backward into their life history. The conceptual starting point has been traced back to the embryonic fetus and even to the fertilized ova by some workers. Interesting and possibly significant research into the origin of patterns of response in embryos already has been done,[1] but its validation and implementation lies in the future. At present, the clinically feasible starting point for understanding and influencing the developing human being is in the obstetric clinic.

The morphology and function of childbearing is essentially the same in all ethnic, racial, and cultural groups within the human species.[2] Conception, pregnancy, and parturition are experiences of adult women whose genetic and developmental history has already significantly structured their personality and delineated the outward limits of their optimism or pessimism, their security or anxiety.

We would expect that, regardless of differences in environment or clinical practice. there would be many universals wherever childbirth is studied. The implications of a survey on a program for training for childbirth, therefore, go beyond its particular practices. In fact, our observations in certain respects do not differ from reports of clinics where more traditional obstetric procedures are used.

Childbearing—one of the most emotionally charged of all human experiences—was the last of the medical specialties oriented toward a psychosomatic approach in its modern phase. Grantly Dick Read's[3] "fear-tension-pain" theory forced the obstetrician and psychiatrist to scrutinize the pregnant woman in her whole state, and not as previously from their widely separated orientations and operational concepts. Under the impetus generated by his work, parallel observations were started in various clinics, each unaware of the others' activities and results. There was advantage in this in that we are able to compare our observations without previous contamination. For example, our findings of a remarkably high level of anxiety and an incidence of social and familial problems might have led us to suspect a methodological error or observational bias if it had not been so uniformly reported in other studies not seen by us. The monograph by Klein, Potter, and Dyk[4] and the comprehensive work of Kroger and Freed[5] have brought psychosomatic observations in obstetrics to a promising level.

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PROGRAM AIMS

The extremes of unwarranted optimism and skepticism with which this program has been greeted have made it as important to point out what it is not as to discuss what it is. A more apt title for this paper might be "Training for Childbirth: Conceptions and Misconceptions."

The program does not seek painless, or primitive, or hypnotic, or even natural childbirth.* Nor is it primarily intended to eliminate anesthesia or to assure consciousness at birth.

It does aim at providing the optimum conditions for a subjectively happy as well as medically satisfactory pregnancy and delivery. This would seem to be an absurdly simple and self-evident proposition. It has significance and novelty only if we are aware of the internalized anxieties that pregnant women bring to

*A paper, entitled "Is Natural Childbirth Natural?" was published several years ago.[6] This title represents an inaccurate question based on a misconception. The question, while intriguing, illustrates a common error concerning this program, one that we ourselves made in its early stages. We no longer seek or speak of "natural childbirth"; the quality of "naturalness" remains unsolved philosophically and indefinable semantically.

the delivery room and of the reinforcing effect on such anxieties produced by contemporary cultural attitudes, misconceptions, and traditional obstetric procedures.

Childbirth is virtually the only nonpathological process that is treated by doctors in a hospital. The orientation of most physicians by education, clinical training, and professional conditioning is to think in terms of pathology. Mothers on their part identify the doctor as one who treats the sick. When, for example, we asked them what they considered most satisfactory in a physician, they spoke in terms of cure of illness and relief of anxiety. They associate hospitals with the care of the diseased and frequently with death.

Yet, the practice of obstetrics in the overwhelming majority of cases deals with the medically "normal." Pregnancy in most instances is a physiological function occurring in a reasonably healthy woman. She shows neither anatomic disproportion, biochemical imbalance, nor any other frankly pathological complications.

This program is an obstetric procedure and is carried out by obstetricians. The psychological and pediatric involvement in this program has been peripheral and observational. The background for the program of training for childbirth is pragmatic and clinical rather than psychological and theoretical. The significance of this is that, while our psychological hypotheses as to its mechanism of action may be questioned, the clinical evidence of its applicability seems by now to be beyond dispute.

This brief discussion is intended neither to report on our research nor to offer clinical validation for our opinions. It is intended rather to present something of the aims, methods, and stresses, as well as the rewards that are part of this program. The validation lies elsewhere—in part, in other reports that have emanated from the clinic,[7-9] from others who have used this method,[3,10] and from studies to follow. Mainly, however, as is always the case, the clinician can test it only by his own observation, practice, and participation in it.

SETTING

Pregnant women who have been cared for by the Obstetrical Department of the Grace-New Haven Community Hospital (University Service) have participated in a program that has prepared them for labor and delivery not only physiologically but psychologically.

The techniques are deceptively, almost naively, simple—education, exercise, reassurance, and considerate, understanding attendance at the delivery. In addition to customary prenatal procedures, prospective mothers attend classes on the normal development of pregnancy and labor. They are trained in exercises to improve their muscular tone and to aid relaxation. They and their husband participate in group discussions led by psychiatrists, pediatricians, and obstetricians. At term, the mother has become familiar with the hospital accommodations, acquainted with the personnel, and oftentimes friendly with many other women in her group.

During labor, the doctors and nurses are able to discuss the mother's progress with her frankly since she has already learned what to expect. They endeavor to offer emotional support and to anticipate possible sources of anxiety. Her husband or other close member of her family is with her during the first stage if she desires, aiding her in using the techniques of relaxation and performing important or small comforting services. Usually she is conscious during the second or delivery stage and often watches and discusses the delivery with the nurse and doctor. Medicaments are administered if she desires them.

Even semantics are affected by this general orientation. For example, the abdominal and uterine contractions are not referred to as "pains," unless they actually hurt, but as "contractions."

In a series of 1,000 cases 95 per cent of mothers having their first child and 97 per cent of those who had delivered before were aware and were participants in the birth of their children. Incidence of complications for both mothers and infants compares very favorably with those in other university clinics.[8]

Our observations come from both obstetrics and psychiatry and are based on clinical obstetric experience during a five year period in a service with an average census of 950, structured psychiatric research on a small group of 30 longitudinally studied patients, and daily psychiatric consultation on the obstetric wards for a period of 18 months. Our sociological concepts are frankly speculative. These data are not differentiated as to source nor statistically presented in this communication.

OBSERVATIONS

How does such a program affect the inter-

action of the patient, doctor, and child? Most of these ordinary clinic patients were functioning adequately as wives, mothers, and homemakers in spite of crippling personal tensions. They told us of social and economic strains and of troubling marital problems of sexual inadequacy and jealousy; they described the whole spectrum of neurotic maladjustments.

Of those who had previously borne children, more than half complained that the earlier deliveries had been excessively painful, distressful, or marred by complications to themselves or their child. Frequently they recalled callous or careless treatment by the medical personnel who attended them. (One mother described with a shudder the murder mystery the intern had tuned in on the radio during her labor). Even those who had not previously borne children were likely to ascribe earlier painful experiences to sexual or gynecologic sources. The severest menstrual difficulties had been endured by the mothers who were emotionally immature and sexually ambivalent. Ignorance or distortion of elementary facts of pregnancy, labor, and even procreation until a relatively late age was the rule. Such knowledge had usually come from outside the home and was steeped in secrecy and guilt.

There had been rejection of pregnancy or the child to some degree at the time the pregnant state was discovered in a majority of the cases amongst both multiparas and primiparas. This was true of all religious groups, the educated and noneducated, and natives as well as immigrants.

Our patients ranged from poverty-ridden, illiterate, and immigrant mothers to the economically, educationally, and socially privileged. Our professional staff is predominantly middle-class, American-born, and, of course, educated.

Initial motivation, identification, and communication were unquestionably influenced by these differences. Some college-educated and career-oriented mothers, often attracted to this plan through reading, ascribed high prestige to the "progressive" doctor and easily, sometimes overeagerly, accepted it. Many in this group had a great need to "do well." Denial of feelings of tension was more common among them. They were more likely to blame themselves if they (as they felt) "failed," although in fact the staff makes no such judgments. The need to master the experiences sometimes resulted in strong conflictual feeling, which the less highly motivated, less "identified" women did not share. There were also differences in the kind and manner of verbalization of their feelings, especially of fear, anxiety, or pain. What is more, the capacity to express direct aggression against the clinic personnel was more inhibited.

The middle-class and upper-class mother in our culture has tended to look on her pregnancy as a rather mysterious process that manifests itself by annoying and socially distressing anatomic and physiological changes. She not infrequently developed a galaxy of "queer" tastes and attitudes, which were not explained or indeed considered explainable.

The puritan tradition among other things in the United States has operated to make pregnancy socially awkward, often embarrassing. Sexuality is still a major taboo of our culture and an unseemly display of gestation has been a not infrequent source of social anxiety.

Activities were likely to be curtailed before this was medically indicated because of the tension engendered in the mother, husband, and community.

In certain economically deprived groups, pregnancy was not considered socially awkward but functionally handicapping. Not infrequently it was looked on as an almost inevitable consequence of marital relationship ("I got caught"), especially as the number of children increased and the mother aged. It was reacted to with varying degrees of stoicism and emotionality, depending on the personality and cultural milieu of the mother.

The less well-educated and immigrant groups tended to follow their more accustomed patterns. They seemed more inclined or capable of turning their aggression outward. Communication between them and the physician was often awkward or difficult. There were more frequent blocks in the transmission of ideas and feelings.

Significantly, however, these differences did not seem to result in ascertainable variations between these groups as to the ease or difficulty of their labor. Apparently, regardless of such cultural differences, more deeply seated personality factors influencing anxiety and emotional stability and the adaptational mechanisms are the important determinants.

Against this background of anxiety, social and sexual misinformation, and ambivalence, the task of the obstetrician is challenging. How does the training program assist him?

Clinical Factors. The period of prenatal training is a reciprocal interacting process involving the hospital staff no less than the parturient mother.

There are blocks in communication between patient, physician, and nurse caused by cultural or semantic differences, or neurotic determinants on both sides of the interpersonal exchange. One of the most important functions of the training program is to discover and eliminate these disturbances in communication and open new channels for interaction.

Unless the doctor and nurse are intimately conversant with the personal and obstetric history of the patient, they will be unable to understand and allay apprehension, even if they do observe evidences of it. Describing her delivery, one mother said, "It was over . . . then I became quite anxious . . . I asked quite a few times if the baby was all right. I was apprehensive even though I could see he was all right." What is striking is that the great rush of nervousness came after the successful and uneventful birth of her child. One could better understand this seeming paradox if it were known that her previous child had numerous anomalies and died a few hours after birth. At this level, those attending her were aware of these tragic events; in fact, they had anticipated her reaction and reassured her with considerable success.

To comprehend the response of this mother fully one needs to know the following facts. The patient had an identical twin sister; the girls' mother died when they were infants and their father, a kindly but extroverted and insensitive man, was "mother and father" to them. The patient's childhood, while generally happy, was charged with an intense competition between her sister and herself in everything, especially for the affection and approval of the father. Her sister had married first (an engineer), and two months later the patient had married his fraternity brother, a philosophy student. The father was delighted and accepting of his bluff, outgoing engineer son-in-law; baffled, dismayed, and rejecting of the intellectual, introverted philosopher. The intense, competitive, sisterly internecine warfare for the affection of the father that had gone on all their lives now extended to their husbands, their pregnancies, and their children. Her sister has had two babies, physically perfect. It was desperately important to our patient to have a whole baby successfully—to prove herself and her husband.

An interesting postscript is that months later she came back for psychotherapy for herself, a necessity precipitated by the fact that her sister was then suffering a postpartum psychosis.

We find that doctors and nurses tend to share values and observational biases with each other. Usually they agree with each other far more than with the mother. Occasionally they differ among themselves in values and judgments, and their interpersonal communication is interfered with.

The nurse often demonstrated a greater sensivity and capacity for sympathy with another woman in labor and showed more awareness of small, homely, but important events, which the doctor in his briefer contacts overlooked. Occasionally, communications directed to the nurse were deliberately withheld from the doctor. Just before delivery, a mother said to her nurse, "I hope he doesn't have feet like mine." This might be merely an amusing example of displaced apprehension concerning body image except that this mother was a fair, blonde, German war bride married to a Negro GI. Until she made this remark she had never verbalized concern over this, although (ironically enough) her life in this country was made hideous by racial bigotry. Immediately after her baby was born she very quietly asked, "What color is it?" None of this was heard by the doctor, nor had the mother intended that it should be. His report, quite accurately describing what he had observed, stated, "Mrs. K. was confident, tense, but cooperative. She reacted with pleasure about the birth of her baby and complained of no discomfort."

Not infrequently, however, it was the doctor who was more empathic and intuitively reactive, and the mother on her side more readily related to a father (or husband) surrogate than to a female figure.

Unless they could be made aware of it, countertransference, positive or negative, affected the treatment as well as the judgments of the doctors and nurses. A young intern who had conscientiously, perhaps overconscientiously, attended an attractive, seductively dependent, hysterical mother discovered to his dismay that after some hours of this she treated him as she had been accustomed to handle her husband. He turned over the case to another physician; intuitively, the physician was aware that here the transference hindered his medical treatment. Resigned and

somewhat baffled, he said, "I guess I sat with her so long I lost my professional relationship."

Sometimes there were moments of excitement, elation, depression, or pain that were unknown to any member of the staff. There were subtle, but significant, discrepancies between the mother's recollection about what her feelings and behavior had been and the observations made by the doctors and nurses attending her. Mothers were likely to tell us that they had experienced less anxiety and discomfort than it seemed to the staff that they had suffered. They rated themselves as complaining less, requiring less emotional support, and being more co-operative than, in fact, they had been.

Even at a superficial level, the obstetrician may make helpful predictions as to the most desirable way to treat certain patients if communication has been established. For example, some of our patients indicated during the prenatal period that they had great difficulty relating to people when under stresses such as pain and resented guidance or instruction at this time. Others almost indiscriminantly wanted companionship and assistance. The patients who later made complaint about the behavior of members of the staff toward them during delivery were those who had previously indicated most strongly their difficulty in accepting the dependent role. For example, one mother described her irritation when encouraged by the nurse to "push." She said, "I knew I should anyhow, and it irritated me to hear her say this; I almost told her to go."

The Husband. The husband, by his attendance at lectures and participation in group discussions, and because of the supporting, comforting role he plays during labor, has become more intimately involved in the birth process than at any time in the recent history of our culture. His role in this is considered both by him and his wife to provide strong mutual support and to facilitate greatly the critical transition from a couple to a family.

The shifting relationship between mother and father in regard to childbirth is amusingly, if extremely illustrated, in the following incident. During a group session we had discussed the sense of isolation that many husbands feel when their wives become pregnant. A young man asked in a puzzled tone of voice whether this was very common since he did not "feel left out at all." He said, "I feel very much a part of my wife's pregnancy." This was discussed in the light of his participation in our program. However, later his wife came to me and said, "I wasn't surprised when my husband said that he feels very much a part of my pregnancy. In fact, ever since we first found out about it, he's been mainly concerned with the baby and with fixing up its room, buying toys and clothes, and making plans. I'm the one that's left out of this pregnancy." While extreme, this is certainly not atypical. It betokens a trend toward male involvement in birth procedures and domestic responsibility generally that was neither created nor discovered by the Training for Childbirth program. It has simply become focused and constructively integrated into the labor and delivery. Its sociological implications are fascinating and will be discussed in a later communication.

DISCUSSION

Read hypothesized that fears, usually of an irrational nature, lead to physiological tension. This tension, in turn, results in interference with easy, rhythmic expulsive function during labor and is responsible for much of the pain that ensues. He and subsequent authors have emphasized the psychological advantages associated with consciousness at childbirth. By and large, our experience confirms these observations. However, in this communication, we have deliberately emphasized the anxieties we have uncovered and some of the difficulties encountered in overcoming them. We have stressed the strains that arise within the program itself. Training for Childbirth is not a finished program. Like psychiatry and the social sciences, it is an evolving system.

In a recently reported study, my colleagues and I (L.Z.F.) studied memory of the events of childbirth, to discern areas and sources of anxiety.[7] Contrary to the expectation of popular mythology, we discovered no gross generalized amnestic process peculiar to labor. Nor could such factors as the intensity of the reported malaise or pain be correlated with the degree of distortion of memory. Nor was there more forgetting of the incidents in a rejected pregnancy than in an apparently accepted one. There were transient distortions and variations in recollection, subtle but significant. Forgetting occurred when a mother found herself in an extremely stressful situation, but the stress or pain in itself seemingly was not the determinant. Repression occurred when the stressful or painful stimulus was part

of a strongly conflictual situation in which she was unable to solve the dilemma by any kind of adaptive behavior. Fear, that is, focused tension, which could be acted upon, or somehow handled in the ego-syntonic economy, was retained. Anxiety-laden areas, that is, conflict situations in which opportunity for adaptive behavior was lacking, tended to be forgotten or distorted.

Our hypothesis as to the reason for the substantial recollection of events is also a hypothesis as to the mechanism of operation in our program: the uncanny and mysterious was made known; a channel for interpersonal communication was opened; and a medium for adaptive behavior was provided. This reduced the need for suppressive or for repressive mechanisms.

The most common criticism of this program is that it is simply a form of suggestion[11] or of suggestion and hypnosis.[6] In our opinion, this demonstrates a lack of understanding of the meaning of these terms as well as the conditions of ordinary interpersonal relationships. This is not hypnosis; however, suggestion, the uncritical acceptance or rejection of another's ideas, is present to some degree in all patient-physician relationships. In fact, to use a regressive metaphor, we are constantly bathed in an ocean of suggestion in all our human relationships. We have cited the innumerable negatively suggestive stimuli in our culture which increase fear of pregnancy. Quite possibly one of the important contributions of Training for Childbirth is to provide the framework for a form of countersuggestion—not only does it supply a rational bulwark against irrational misinformation but also conscious and unconscious ego support—countering the conscious and unconscious infantile and contemporarily induced anxieties of the patient.

Avenues for adaptive behavior, constructive countersuggestion, support, and channels for communication seem to be the key factors in the functioning of the program.

It opens up channels for communication that hitherto have been damned by professional tradition and social taboo of mothers and doctors. Even the baby lets out his first howl sooner and louder than in the days when his first breath of air was choked with asphyxiating fumes.

For the mother it means preparation for childbirth, consciousness during it, and frequently the fulfillment of a personal achievement rather than a function of mechanical transmission.

For the husband it gives focus to his role in the home; it protects him from alienation and frustration that progressively have been his role.

The clinician widens his perspective from viewing his patient as a pelvic dimension to a person with a developmental history and emotions. The program has meaning and promise as it introduces a kind of psychological humanism as well as determinism into the obstetric clinic.

The rewards to the infant must still be speculative—we cannot ask him. We can only record the freedom from transient asphyxiation that had almost invariably accompanied anesthetic deliveries and the presence of a consciously responding mother to take him to her breast at once. We shall learn more about this as time goes on, for long-range observations are now being made by other groups at Yale.

Training for Childbirth is obviously only one facet in the unity of human mating, conceiving, bearing, and growing. Conception, fruition, and delivery are unitary, not isolated. Correspondingly, in the ultimate assessment, insights gained through the interpenetration of the specialties concerned with the care of our patients may be the most significant and lasting contributions of this program.

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Some Effects of Mineral Elements in Nutrition*

Thomas H. Jukes, Ph.D.

THE NEED FOR MINERALS in nutrition is a reminder that life first evolved in contact with the oceans. The major minerals in our blood stream are similar in their proportions and balance to those found in a more concentrated form in sea water. This balance must be carefully regulated for the body to function normally; for example, the right concentrations of potassium, sodium, and magnesium are necessary for the proper functioning of muscles, including the heart muscle. The essential minerals are found in all forms of animal life, and special functions for certain minerals are seen in the higher animals; for example, as the lower forms of life evolved to become more complex, biochemical mechanisms appeared for concentrating calcium carbonate and crystallizing it in a solid form. The shells of oysters and clams are formed by this means. A further step in evolution was the deposition of calcium phosphate to form the bony structures of vertebrate animals.

Sea water contains, in addition to such minerals as salt, magnesium, potassium, and calcium, a wide range of the so-called trace minerals. These are inorganic substances found in living organisms in small amounts. Some of these trace elements have no known functions in nutrition, but others are needed in the diet. Doubtless this need was developed by the appearance of specific organic compounds during evolution. Even today, we are constantly reminded of the marine origin of animal life by the occurrence of hypothyroidism in regions far from the sea. This is due to a deficiency of iodine, one of the elements of sea water. Iodine is essential to the functioning of the thyroid gland, and animals living close to the ocean or consuming marine products do not develop hypothyroidism. Plants have never developed a need for iodine, but in most other cases the trace elements needed by animals are essential to plant life and are present in plant products. This circumstance helps to solve some of the problems of mineral nutrition of animals, but there are also the following questions to be answered: (1) the difficulty of absorbing certain mineral elements through the wall of the intestine into the blood stream because of insolubilities of these minerals in the intestinal contents; and (2) how to supply the quantitative requirements of animals for minerals with the amounts in foods of vegetable origin.

The minerals needed by animals are usually divided into two groups. The first group consists of calcium, sodium, magnesium, potassium, phosphate, chloride, sulfate, and carbonate. These are necessary in the blood and tissue fluids for preserving osmotic pressure, maintaining the correct *p*H, and providing the correct ionic environment for the functioning of protoplasm. They are required in comparatively large amounts. The other essential minerals are usually termed the trace minerals and include: iron, copper, manganese, zinc, cobalt, molybdenum, iodine, and possibly selenium. All of these except iodine, cobalt, and selenium are needed by plants; there are certain trace minerals such as boron and vanadium that also are needed by plants but are not known to be required by animals. Fluorine is of importance in animal nutrition primarily because of the toxic effects produced by feeding amounts greater than 50 ppm. In human nutrition, a deficiency of fluorine may lead to the development of dental caries, although excessive amounts have deleterious effects.

Some of the trace minerals are metals that can exist in more than one state of valence so that they can participate in the transfer of electrons in reversible oxidation systems. The most prominent of such systems is that involv-

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ing the cytochromes. These substances contain iron that alternates between the ferrous and ferric states; by this means, oxidation of foodstuffs is brought about through a succession of steps that convert carbon and hydrogen to carbon dioxide and water.

A large part of the research in modern biochemistry is concerned with the study of isolated enzyme systems, and many interesting facts have been revealed. As an example, a step in the metabolism of fats takes place when butyric acid combines with a molecule containing pantothenic acid to form "butyryl coenzyme A." This compound is then dehydrogenated by butyryl dehydrogenase, an enzyme containing riboflavin, so that in this step two vitamins simultaneously participate. Iodine is a component of the thyroid hormone which is concerned with the enzymatic oxidation of foods in some unknown manner. Such observations of the actual mechanism of the action of vitamins and minerals are a possible clue to the pathological changes that take place in dietary deficiencies, and it is most interesting to note that some vitamin deficiencies produce changes that resemble those seen in mineral deficiencies. For example, a bone deformity called perosis can be produced in birds by a deficiency of manganese or by a deficiency of some of the vitamins, and dermatitis in pigs can result either from zinc deficiency or pantothenic acid deficiency.

One of the most interesting and intricate functions of trace mineral metals is their action in enzyme systems. There are two groups of enzyme systems with metallic components: (1) enzymes that are activated by metals, and (2) enzymes that contain a metal as part of the molecule. In the first class are enzymes concerned with the transfer of phosphate. Prominent among these enzymes are the kinases and phosphorylases, which transform sugars to sugar phosphates. Magnesium activates these enzymes, and this property is shared to some extent by manganese. In the second class are such enzymes as carbonic anhydrase and other enzymes, which contain zinc; the peroxidases, which contain iron; and some oxidizing enzymes such as aldehyde oxidase, which contain molybdenum. Examples of enzymes in both these classes are seen in table I.

An important practical difference between vitamins and minerals in nutrition lies in the fact that high levels of the essential minerals are often not well tolerated or are even toxic. This situation may be encountered when the level of the mineral is only a few times greater than the level ordinarily ingested. Such a situation is not encountered with the vita-

TABLE I

Enzymes with Metallic Components

Element	Enzyme	Occurence	Reaction
Zinc	Carbonic anhydrase	Lung, kidney	$H_2CO_3 \rightarrow CO_2 + H_2O$
	Peptidases	Various tissues	Peptides→amino acids
	Alcohol dehydrogenases	Liver, yeast	Alcohol→aldehyde
	Glutamic dehydrogenase	Liver	Glutamate→ketoglutarate
	Lactic dehydrogenase	Liver	Lactate→pyruvate
Iron	Cytochromes	Tissues	Electron transport, such as, reduction of riboflavin
	Catalase	Blood	$2H_2O_2 \rightarrow 2H_2O + O_2$
	Peroxidase	Tissues	Catechols→orthoquinones
Manganese	Oxalosuccinic decarboxylase	Liver	Oxalosuccinate→ketoglutarate
	Oxaloacetate decarboxylase	Liver	Oxaloacetate→pyruvate
	Arginase	Liver	Arginine→ornithine
Copper	Uricase	Kidney	Uric acid→allantoin
	Tyrosinase	Skin	Tyrosine→DOPA quinone
Molybdenum	Xanthine oxidase	Liver	Xanthine→uric acid
	Aldehyde oxidase	Liver	Acetaldehyde→acetate
Magnesium	Phosphorylases, kinases	Tissues	Sugar + PO_4→sugar phosphate
	Creatine kinase	Muscle	Creatine→phosphocreatine

TABLE II

Effects of Deficiency and Excess of Various Mineral Elements in Animals

Element	Effects of Deficiency	Effects of Excess
Iron	Hypochromic anemia	Hemosiderosis, cirrhosis
Copper	Hypochromic anemia, nerve lesions	Hemolytic jaundice, liver atrophy
Fluorine	Dental caries in human beings	Mottled and brittle teeth, bone damage
Cobalt	Vitamin B_{12} deficiency in ruminants	Polycythemia
Manganese	Reproductive disturbances, perosis	Tremors, cirrhosis
Magnesium	Convulsions	Narcosis (when injected)
Zinc	Parakeratosis in pigs	Slow growth, anemia, reproductive failure
Molybdenum	Slow growth in chicks	Cardiac lesions, anemia, defective hair formation
Iodine	Goiter, myxedema	
Selenium	Exudative diathesis in chicks, liver necrosis in rats	"Blind staggers," lameness, loss of hair, atrophy of heart and liver
Potassium	Slow growth in chicks	
Sulfate	Slow growth in chicks	Diarrhea

mins unless the levels fed are many times greater than the amounts occurring in the daily diet. Some examples of the toxic effects of excessive quantities of the essential minerals are listed in table II, together with the effects of their deficiencies. Certain minerals tend to accumulate in the body when large quantities are fed, and this fact contributes substantially to the toxicity of excessive levels of such minerals.

Experiments in animal nutrition have led to a number of recent observations regarding trace minerals. It has been possible to explore the field much more easily with experimental animals than by means of studies in human nutrition.

COPPER

Deficiencies of copper are well known in farm livestock and in laboratory animals. Young rats and pigs readily develop a nutritional anemia on diets of milk supplemented with pure iron salts. However, it appears to be difficult or impossible to produce an anemia in human beings that is due to copper deficiency.

The amount of copper in the tissues of the human being is quite appreciable, about 1.5 to 2.0 mg. of copper per Kg. of body weight. The blood contains about 0.1 mg. of copper per 100 cc., and about four times this level is present in the liver.

Various studies with experimental animals have shown that the amount of copper present in the liver is regulated by the amount in the diet. Ruminating animals such as sheep are quite sensitive to dietary changes as regards the body storage of copper; for example, the amount of copper in the liver of sheep is affected by the dietary intake of molybdenum and sulfate, both of which occur in natural foods. Nonruminating animals are probably less susceptible to such variations in the composition of the diet. The amount and form of copper in the blood is of great clinical and biochemical interest. Two copper-containing proteins are present in the blood. The first is hemocuprein, which is present in the red blood cells, and the second is ceruloplasmin, a blue protein occurring in small amounts in the blood plasma. Apparently the level of ceruloplasmin in the blood is of importance in controlling the metabolism of copper, and 90 per cent of the copper in the blood plasma normally is in the form of ceruloplasmin in which the copper is firmly bound. It has been shown that in Wilson-Uzman's disease (hepatolenticular degeneration) the level of ceruloplasmin is gradually reduced and the free plasma copper increased. Cirrhosis of the liver and kidney degeneration are developed, and this is thought to be due to the injurious effects of the free "unbound" copper. Recently, penicillamine has been used to treat hepatolenticular degeneration by its property of combining with the free copper

in the blood plasma, thus preventing the toxic effects of excessive levels of uncombined copper ions.

MOLYBDENUM

This element recently has been shown to be a component of certain enzymes in the body, specifically xanthine oxidase and acetaldehyde dehydrogenase. The level of xanthine oxidase in the liver of experimental animals is markedly reduced on a diet deficient in molybdenum; however, the amounts needed are extremely small, and 0.02 part of molybdenum per million of diet in the diet of rats is said to be sufficient to produce normal levels of xanthine oxidase. Many foods contain at least 10 times this amount. No ill-effects of molybdenum deficiency have been shown for experimental animals or for human beings.

Molybdenum is important in the nutrition of ruminating animals since these animals are susceptible to the toxic effects of crops grown on soils with a high content of molybdenum. These toxic effects are counteracted by feeding copper sulfate. The relationships between molybdenum, copper, and sulfate in the nutrition of ruminants are complicated and are being studied by various investigators.

ZINC

Appreciable amounts of zinc are present in the body; in fact, the total amount is almost one-half as great as that of iron. The internal organs and the epidermal structures contain more zinc than do the other tissues. Zinc is a component of an important enzyme, carbonic anhydrase, which regulates the liberation of carbon dioxide from the blood into the expired air through the lungs. Carbonic anhydrase is also important in controlling diuresis. The zinc present in the red blood cells appears to be entirely in the form of carbonic anhydrase. There is much interest in zinc in animal nutrition, because a few years ago it was shown that a disease of pigs called parakeratosis could be cured by feeding zinc sulfate. This disease is characterized by slow growth and an acute and widespread dermatitis. It is aggravated by feeding excessive amounts of calcium carbonate. The alleviative effects of zinc in this disease solved a mystery that had existed for some years in animal husbandry. As so often happens, the disease was presumed to have an infectious origin when the actual cause was nutritional. Many experiments were made to investigate possibilities that viruses or parasites were responsible for parakeratosis in pigs. Eventually it was found that mixtures of salts of the trace elements would cure the condition, and it was then shown that zinc sulfate was the beneficial component of such mixtures. This was surprising because the animals with the disease had received diets that contained presumably adequate amounts of zinc; for example, some of the diets on which pigs developed parakeratosis contained as high as 20 ppm of zinc, which should have been sufficient in view of the fact that rats do not develop zinc deficiency readily unless the diet contains less than 2 ppm of this element. Apparently the presence of calcium carbonate as an additive in the diets of the pigs interfered with the utilization of zinc in the digestive tract.

COBALT

The importance of cobalt in nutrition was recognized only after a long series of investigations, which led to the solving of a scientific mystery that had existed for many years.

Certain areas in various parts of the world were known to produce crops upon which sheep and cattle were unable to thrive; however, horses and rabbits were able to consume these crops and remain in good health. The disease developed by the sheep and cattle was marked by loss of appetite, emaciation, and anemia, culminating in death. The presence of anemia led to the idea that the disease was due to iron deficiency, and the animals were found to respond to dosage with crude salts of iron. However, it was subsequently found that the tissues of the sick animals contained larger than usual amounts of iron, and it was discovered that an iron-free extract of certain crude iron salts would produce a cure in the animals. It was then found that the curative substance was cobalt, which had been present as a contaminant in the crude iron salts. The addition of small amounts of cobalt to the soils was sufficient to control the disease by maintaining adequate cobalt levels in the crops grown on the formerly deficient soils. Liver extract also had a curative effect. In 1948 the antipernicious anemia factor in liver extract was shown to be a compound of cobalt. It was then demonstrated that this compound, vitamin B_{12}, was able to cure the disease of ruminants when injected. This and other experiments made it clear that in the

absence of cobalt the ruminants were unable to obtain vitamin B_{12} by fermentation in their digestive tracts, and that the addition of cobalt to the feed corrected this deficiency by restoring the ability of the rumen bacteria to produce the vitamin.

The essential nature of cobalt in nutrition appears solely to be due to its presence in the molecule of the antipernicious anemia factor, vitamin B_{12}. This vitamin is needed by all animals, and it is not normally present in the higher plants. Animals are dependent on bacteria and moldlike organisms for their supplies of vitamin B_{12}. These microorganisms in turn need cobalt for their manufacture of the vitamin, which contains 4 per cent of cobalt. Ruminating animals obtain vitamin B_{12} from the natural fermentation that takes place in their paunch, where numerous species of bacteria synthesize vitamin B_{12} and other necessary vitamins. Carnivorous animals obtain most of their supply of vitamin B_{12} by devouring foods of animal origin such as meat and fish in which the vitamin has been obtained from other food sources and stored in the tissues.

Excessive amounts of inorganic cobalt salts have a pharmacological effect and produce a polycythemia. The exact mechanism for this stimulation of blood-cell-forming mechanism is unknown but it appears to have no relationship to vitamin B_{12}.

MANGANESE

All animal tissues contain manganese in very low concentrations, and it is known to be concerned in a number of enzyme systems including phosphatase, arginase, and certain peptidases. Manganese deficiency produces remarkable bone deformities in birds. These deformities include chondrodystrophy in embryos and perosis, a shortening and twisting of the leg bones in growing birds. Reproductive disturbances are produced by manganese deficiency in rats on experimental diets. No effects of manganese deficiency have been noted in human subjects, and it seems probable that ample amounts of this element are present in natural diets.

IODINE

Iodine is needed by animals because it is an ingredient of the thyroid hormone. This hormone contains thyroxine and triiodothyronine, both of which contain iodinated phenolic groupings. A deficiency of iodine results in an outbreak of endemic goiter in human beings and animals. This was discovered a long time ago and the acceptance of this fact took many years of educational effort, but today the addition of iodine to common salt is universally accepted as a public health practice for the prevention of endemic goiter.

Iodine combines in the thyroid gland with a derivative of tyrosine to form two amino acids, thyroxine and triiodothyronine. These two compounds in the form of protein conjugates are responsible for the activity of the thyroid gland in controlling the metabolism of various foodstuffs.

The thyroid gland has the remarkable property of being able to bring about the concentration of iodides from the circulating blood. About 30 per cent of the total amount of iodine present in an adult human being is in the thyroid gland, even though this gland represents only 0.2 per cent of the weight of the body. The recommended dietary intake for iodine is about 0.1 to 0.2 mg. daily. Seafood and ocean fish are good sources of the element.

SELENIUM

The presence of excessive quantities of selenium in certain soils, particularly in Wyoming and South Dakota, has led to poisoning of livestock that graze in these areas, and for many years selenium was considered solely as a toxic element.

In 1957 it was found that small traces of selenium may be of importance in nutrition, although amounts in excess of 5 ppm in the diet of animals are toxic. This discovery was another scientific detective story. Certain diets were known to be injurious to rats, and these animals developed liver necrosis on these diets, which contained yeast as the source of protein. However, only certain batches or types of yeast would produce the injurious condition, and then only in the absence of vitamin E. The dietary liver necrosis could be prevented not only by vitamin E but also by feeding natural foods that contained no vitamin E. An analogous disease was produced experimentally in chickens by feeding them similar diets. These animals developed exudative diathesis rather than liver necrosis (Fig. 1). The unidentified factor in natural foods was found to be present in the ash produced by burning the foods to completion in the presence of calcium oxide. It was then

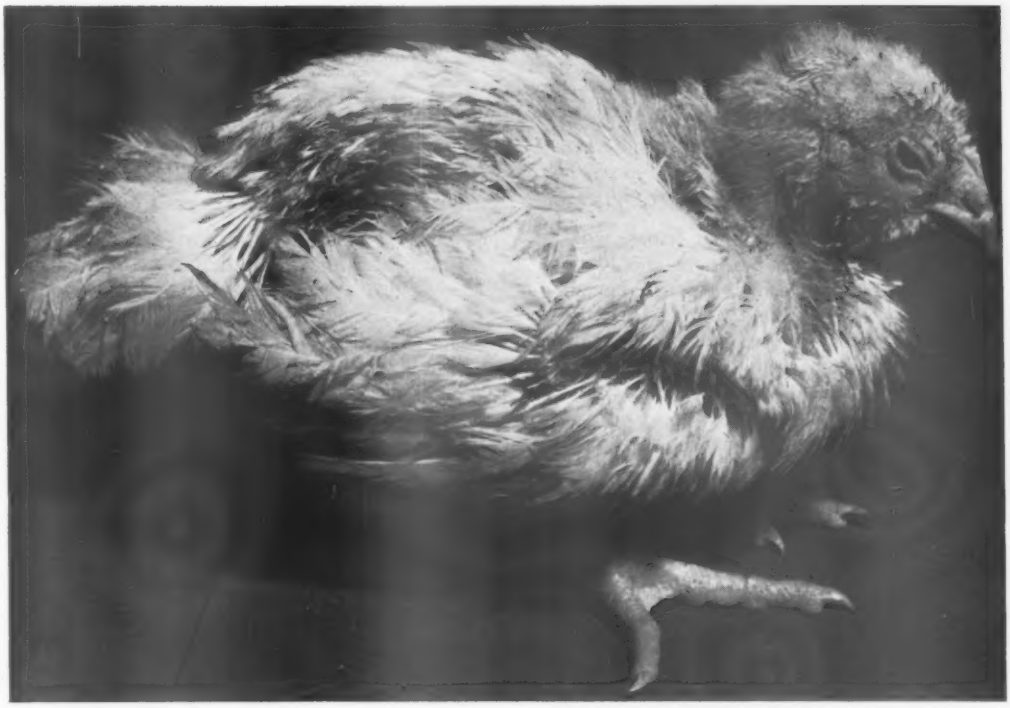

Fig. I. Exudative diathesis in a chick aged 25 days, produced by feeding a diet containing prnicipally glucose and Torula yeast. The condition may be prevented by adding selenium to the diet (Patterson, E. L.; Milstrey, R., and Stokstad, E. L.: Effect of selenium in preventing exudative diathesis in chicks, Proc. Soc. Exper. Biol. & Med. 95:617-620, Aug.-Sept., 1957.

found in two series of experiments, one in the laboratories of the National Institutes of Health and the second in the research laboratories of the American Cyanamid Company, that selenium in the form of sodium selenite was protective. Further experiments with chicks indicated that the beneficial level of selenium was in the range of 0.1 to 0.3 ppm of diet, while the toxic range was not reached until approximately 50 to 100 times this level was fed in the diet.

Nothing is known of selenium in human nutrition. The toxic properties of this element are well recognized, but it appears that it may have an essential role in the biochemistry of the body at minute and subtoxic levels.

The Female Patient Who Works

Beatrice Mintz, M.D., M.P.H.

THE SPECIAL PROBLEMS of the female worker who presents herself as a patient should need no exposition to the female doctor, herself a worker, but, since female doctors may look on themselves as superwomen and possibly function in somewhat unique social and occupational environments, it may be well to examine some of the broad implications for health maintenance inherent in the general working situation.

THE FEMALE LABOR FORCE*

The chances of a female patient being a worker* have been increasing each year as more and more women seek employment out of the home. Five million women, or 18 per cent of the adult female population, were working in 1900.[1] In 1956 the proportion had practically doubled, with almost 22 million working or seeking work at any one time. Figures available in 1957 indicated that the number would be still higher by the end of December, 1957, if present trends continued.[2]

These figures, however, do not tell the whole story. Many women go in and out of the labor force during any one year because of the seasonal character of their work and for personal and family reasons, so that the number who actually have work experience in any given year may exceed by several million the number found working. In 1955, for example, the female labor force amounted to almost 21 million. In contrast, the Census Bureau reported that about 28 million women had worked during the year.[3] This latter figure was a sizable proportion (approximately 46 per cent) of the adult female population. It was also a significant part of the nation's entire civilian labor force—66 million that year.

These women can not all be young and single with responsibilities only for themselves. Not only is the now prevalent earlier marriage age decreasing the number of young single workers in the labor population, but various social forces are operating to bring married women with growing children and older women whose children have reached adulthood into the labor market. In 1955 only 25 per cent of the working women were single. Over one-half were married and living with their husbands, and 33 per cent (including many with no husbands present) had children under 18 years.[4] The significance of this distribution on the over-all problems that female workers may bring their doctors for solution cannot be minimized.

WHY WOMEN WORK

Inseparably linked to the afore-mentioned, and of equal importance for a fuller understanding of those problems, is the question of why women work. Economic necessity was assumed, and rightly so, in the case of mothers and children who manned machines in the early days of the textile industry in this country. The domestic worker who today leaves her children alone while she cares for other people's is likewise assumed to need the money. That the same motivations apply to wider segments of the female working population is a more recent conception. Of 20 million working women, almost 2.5 million were classified by the Census Bureau as family heads and another 10.5 million were contributing to the family income in spite of the fact that they were living with their husbands. About 5 per cent of those living with their husbands were, in fact, the sole earners in the family. The remaining 7 million working women either had no relationship to a family group or were family members such as

*"Labor Force" is used in the Census Bureau's meaning of those working or seeking work. "Worker" in this paper is restricted to one who works for pay or in a family enterprise.

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daughters, sisters, grandmothers, and so forth, who conceivably were forced by circumstances to support themselves.[5]

Implicit in these figures is a refutation of the time-honored thesis that women work for "pin money." More intensive studies have documented this fact even further. One of these, a 1954 Census survey, has shown that, in families where the wife was working, the median income was $5,336, with 27 per cent having $7,000 or over. On the other hand, in families where the wife was not in the labor force, the median was $4,051 and only 15 per cent were in the higher income bracket mentioned.[6] At current price levels, it is apparent that even where women do not provide solely for their own or their family's support, their contributions in the main are needed supplements for the purchase of necessities or to maintain that higher standard of living considered an American birthright.

Our present economy, in addition to making paid employment an indispensable condition of existence for so many, has been responsible for other developments affecting woman's work.[7] It has created increasing employment opportunities so that fewer women need be in agriculture and domestic service and more can be professional and clerical workers. At the same time, it is altering the cultural milieu to the extent of making work outside the home more acceptable to female workers and to the rest of society, regardless of whether the ensuing income is a necessity. Work outside the home, in becoming socially more acceptable, is proving important to many more women as a means of self-fulfillment and satisfaction, and consequently becomes a necessity for them.

WORK AND HEALTH

Clinical medicine has learned to consider a patient's occupation in ferreting out etiological factors. A woman's response to specific occupational hazards appears to differ in no essential from a man's. Where the job is suited to the individual's physique and training, no special results should be expected because the worker happens to be a woman. Even in regard to the matter of pregnancy, how long a pregnant woman continues to work and whether any modifications must be made in her job are questions for individualized management of the particular patient. This does not negate the fact that social attitudes may influence certain aspects of the working environment and the interrelationships of home and work, so that a woman may appear to be affected deleteriously.

It is always a surprise to find that women, who live longer and generally suffer less than men from long-term disability, should lose more time from work because of illness. Results of numerous studies dating back many years are consistent in this respect.* Among the more recent studies is one taken by the Metropolitan Life Insurance Company on its own employees.[8] The incidence of illness lasting eight calendar days or longer was higher for women than for men by a ratio of 1.75:1.00. The excess, although not equal in every age group, was appreciable throughout. The women also lost more time, age for age, but the average period of disability was longer for men than for women, particularly in the 45 to 59 year age group.

Many explanations have been offered for this seeming contradiction between the facts of female mortality and morbidity. In years past when the differences in mortality experiences between the sexes were not so striking, the excess female morbidity was considered a confirmation of what everyone knew anyway —that women were members of the weaker sex. Today, in the light of increased knowledge we look more deeply for reasons. Attitudes toward illness and proper care of oneself and differing threshold levels for minor disabilities come to mind. Actual relationships to female physiology and childbearing functions undoubtedly enter the picture as well, but, perhaps social factors should be explored to a greater extent.

Harassments of the female worker are manifold and create a physical and psychological environment that no doctor can overlook. A not very subtle analysis is required to reveal that the working wife has a dual job and may be physically exhausted, or that the working mother is suffering from worry about the whereabouts of her children during her absence and serious mental conflict over how best she can discharge her duty to them. Discontinuous work experience, likewise, leaves its mark on the woman who returns to paid employment when her children no longer need her. Not only must she, in her maturity, find herself learning again, but chances are

*See U.S. Public Health Service studies of industrial absenteeism appearing in issues of *Public Health Reports* from 1920-1953.

that her supervisors will be young men, not much older than her own children, and that the job she holds will not be commensurate with her potentialities.

Frustrations incidental to dual loyalties to home and work do not beset only wives and mothers. Single women living in family units carry more responsibilities for the functioning of their homes than do comparable male family members. The dead-end jobs, the deserved promotions that go to men instead, and the lower pay scales constitute still other tension-producing situations that may face any woman regardless of marital or maternal status.

"HEALTH PROMOTION" PROGRAMS

The numerous inequities that affect the female worker have been recognized by the National Manpower Council in its recommendations on development and utilization of "womanpower."[9] These recommendations cover such areas as education and training; suggestions to employers for equality of treatment in regard to opportunities and pay, and to unions to seek implementation of such principles; consideration of women's other functions by adjustment of work schedules; and review of the adequacy and consequence of existing federal and state laws as related to the employment of women.

Programs and practices embodying many of these recommendations already exist to varying extents and with diverse success. To the degree that they help eliminate the results of discrimination and unequal bargaining power, they contribute to health and well-being and are valuable tools of preventive medicine. If, in addition, they make it possible for women to fulfill their many functions more satisfactorily, their properties are distinctly therapeutic as well.

Among the oldest and still most widespread of such programs is the body of state laws defining and implementing desirable labor standards for female workers. Massachusetts in 1874 enacted legislation limiting the work week to 60 hours for women and minors. This was the first such law with some elements of enforceability, and it followed more than 40 years of continuous agitation for regulation of hours of all working people.[10] That it, and subsequent hours laws, did not cover men was due to a variety of reasons, foremost among which was the fact that opposition could be overcome most successfully on the plea that women and children required special measures to protect their health and welfare because of their inferior physical stamina. Actually, men, through their unions, had been able to achieve more advantageous working conditions for themselves. They not only did not need legal safeguards to the same extent but also stood to profit by such control over woman's work in the inevitable improvement in their own conditions that would follow the example set by these statutory standards.

Today, legislative control over woman's work may cover not only hours but other elements in the working environment that affect health and welfare. Provisions governing reasonable seating, rest rooms, weight lifting, restrictions against work in specified hazardous or otherwise undesirable occupations, industrial homework, minimum wages, and equal-pay stipulations may be found in the labor laws of the various states and territories and federal government.[11] Some of these laws apply to men as well as to women. Additional ones covering both, such as, Unemployment and Temporary Disability Insurance, Old Age and Survivors Insurance, and Workmen's Compensation Laws, also logically could be included here.

Statutory recognition of the need for maternity protection is found within very few governmental jurisdictions of this country.[12] Six states (Connecticut, Massachusetts, Missouri, New York, Vermont, and Washington) and Puerto Rico prohibit work for a few weeks before and after delivery, but only Puerto Rico goes to the heart of the matter. In addition to mandatory time off, the employer is required to pay the working mother half her regular wage and to hold her job for her during her absence. Cash benefits are also provided under Rhode Island's Temporary Disability Insurance Act and the Federal Railroad Retirement Act. The failure of government action to take care of maternity problems of the female worker is compensated in small part by voluntary arrangements. Workers in private employment may work under collective bargaining agreements or independent employer-personnel policies that provide insurance benefits and job security during maternity leaves. Maternity leaves without pay are recognized practice in public employment.

There are other examples of voluntary practices that help to overcome some of the problem areas. A limited number of day-care

centers for children of working mothers can be found, particularly in large urban centers. Likewise, individual adjustments of working schedules and the provision of desirable working conditions over and above those required by law do exist. How widespread these are and how much they are a part of public policy are largely unanswered questions.

COMMENT

Paid work must be recognized as one of several functions that women perform and will in all probability continue to perform. Women may need work for either the income or the satisfaction it brings or for both. The economy in turn needs female workers. Under these circumstances, no consideration of problems presented by women can overlook this possible facet of their lives. Its implications for health and well-being must be understood, and the interrelationships with other factors influencing health must be evaluated by those charged with medical care of women.

The problems discussed seem to devolve mainly on the unequal position that the working woman occupies with respect to her male counterpart and to the member of her own sex who remains at home with just one job. These difficulties stem not only from the functions women are expected by custom to perform as mothers and homemakers but also from social attitudes and unequal bargaining power at the place of work. Legislative and social practices that secure some compensation for these inequities serve the needs of preventive medicine and help promote the health of the woman who works.

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Accidents

Despite much progress in their prevention, accidents are still the fourth leading cause of death in this country, according to an analysis released by the Health Information Foundation in 1957. The October issue of the Foundation's statistical bulletin, *Progress in Health Services*, points out that the annual number of accidental deaths has remained fairly constant at about 100,000 since 1932. But death rates per 100,000 population have gone down 40 per cent in the last half century. Recent medical advances have had much to do with the improvement.

In addition to the death toll last year, accidents caused 9.5 million injuries and financial losses of over 11.2 billion dollars. This is almost as much as Americans spend on all private medical services in a year, the Foundation notes. "In general, safety against accidents has achieved the greatest success where society has been able to bring organized influence to bear. . . ."

Strict enforcement of safety regulations and the growth of safety consciousness, as well as improved work conditions, living standards, and medical care, has resulted in a sharp decline in deaths from industrial accidents, the Foundation says. Accidental deaths involving railroads and scheduled airlines have also diminished greatly. Less improvement has been shown in the American home, where about 30,000 accidental deaths occur each year. Most of them are caused by falls or fire, with older people and small children the most frequent victims. Although the 1956 motor vehicle death toll, 40,000, was the largest in history, there are signs that automobile travel is becoming safer in terms of actual miles driven. The number of deaths per 100 million miles fell from 16.7 in 1934 to 6.4 in 1955 and 1956.

Although the over-all accident picture has improved, "accident tolls and cost could be reduced further—as could incidence of illness and premature death if the public gave greater attention to preventive health measures, better health habits, and early consultation with physicians."

CASE REPORT

Arachnodactyly (Marfan's Syndrome)

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IN RECENT YEARS INCREASING ATTENTION has been directed to arachnodactyly (Marfan's syndrome). These cases present characteristic skeletal anomalies associated with ocular, cardiac, pulmonary, and connective tissue defects. The syndrome is still considered one of the rare diseases, although over 350 cases[1] have been reported. It occurs in varying degrees from the more severe type with its full complement of manifestations to that with variable isolated components known as the formes frustes. Of considerable importance in diagnosis and therapy is that in this interesting hereditary disease, formes frustes are exceedingly common. When a case of Marfan's syndrome is recognized, the physician should be alerted to the less outstanding and possibly isolated stigmata present in other members of the family. Early recognition of these defects and their significance may lead to more effective treatment of serious cardiovascular, pulmonary, and ocular conditions if they occur. A history of Marfan's syndrome is therefore presented in which the mother, father, and 6 siblings exhibited formes frustes.

CASE REPORT

A 2 year old white girl was admitted to the Woman's Medical College Hospital on Sept. 12, 1955, for study of congenital anomalies. The diagnosis on admission was Marfan's syndrome.

Full-term delivery on July 26, 1953 was normal and spontaneous. There was no cyanosis, jaundice, or respiratory difficulty. She was noted to have exceptionally long fingers and toes and bilateral talipes calcaneus. By comparison, her fingers were approximately 1.5 cm. longer than those of her 17 month old sibling, who was considered normal. At 4 months of age, casts were applied bilaterally to the feet. They were removed at 6 months of age, and, shortly after this, the child began to pull herself up. She walked without support at 1 year. The parents have always considered her to be exceptionally active in comparison with her siblings.

When the patient was approximately 16 months old, her parents noticed that she bent to examine objects at a distance of about 1 inch. An ophthalmologist who examined her when she was 22 months old made a diagnosis of bilateral luxation of the lenses with a high degree of myopia. Glasses were fitted and resulted in marked improvement in her vision so that she recognized her siblings by sight. She became more cheerful and happier.

There were no feeding problems. She had difficulty in passing stools, and her sphincter was dilated with good results; however, she still strained in passing stools. Her mother stated that she was easily trained for both feces and urine by 1 year of age.

Motor development was within normal limits. She walked at 1 year of age, talked early, and had six teeth at 9 months of age. Her weight and height record is shown in table I.

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TABLE I
Record of Height and Weight

Age	Weight, lb. and oz.	Height, in.
At birth	8 and 4.5	19.5
5 wk.	9 and 10	22.25
2 mo.	11 and 1	24
3 mo.	11 and 10	25
6 mo.	16 and 10.5	28
1 yr.	21 and 11	31.5
2 yr.	29	37

The child is amiable and well adjusted and does not present behavior problems. She has had no serious illnesses nor contagious diseases.

The family consists of a father, mother, and 7 children. The mother, aged 32, is 5 feet 4 inches tall and has webbed toes; the father, also aged 32, is 5 feet 11 inches tall and had a double herniorrhaphy. The siblings consist of a girl, aged 10, with webbed toes; an 8 year old boy who had a double inguinal hernia; a boy, aged 6, who has frequent attacks of otitis media; a 5 year old girl with webbed toes who had umbilical hernia that was repaired; a 4 year old girl with webbed toes; and a 2½ month old male sibling with a direct and indirect inguinal hernia and an umbilical hernia. All of the 5 older siblings have speech defects.

Physical examination revealed a tall, thin, asthenic, alert, and cheerful child with wizened facies, appearing older than her actual age of 36 months. She was wearing thick-lensed glasses. She followed directions intelligently, talked, was co-operative, moved actively around her crib, aided in dressing herself, and was well co-ordinated. Her skin was sallow and of good turgor, normal temperature, and normal moisture. Her subcutaneous tissue was sparse and her musculature slight and poorly developed. Posture and gait were normal for her age and scapulae and spinal curves were also normal. The extremities were long and slender, with striking length of phalanges of both fingers and toes. The head was markedly dolichocephalic and the fontanels were closed. Frontal bossing was present and there was shallow bilateral parietal depressions. The head circumference was 21.75 inches; height, 41.5 inches; and span, 41.5 inches (see figure I).

Examination by the ophthalmologist[2] revealed a high degree of myopia. Visual acuity was unobtainable. The external examination was normal and the globes were of normal size. With a widely dilated pupil, both lenses were found to be dislocated upward and the edge of each lens could be seen in the bottom of the pupillary area. The zonule was missing inferiorly. Her refractive error was in the neighborhood of −15.00 sphere in each eye. With suitable glasses the child has adequate vision.

The ears showed prominent, flabby auricles that were within normal size and range. The canal and drums were normal, as was her hearing. The nose examination was also negative. Examination of the mouth revealed thin lips, a high arched palate, a narrow jaw angle, and malocclusion; the teeth were normal. The chest circumference was 20 inches, with expansion to 20.5. There was no marked depression of the sternum.

A slight flaring of the rib cage was noted inferiorly. There was no chondrocostal knobbing. The lungs were normal and the heart showed no prominent vessels on the chest well and no precordial bulge. The apex beat was in the fourth interspace at the nipple line. No murmurs were heard and no cardiac enlargement was found. The rate was 120 per minute and there was a normal sinus rhythm. The abdominal examination was negative except for a palpable liver 2 fingerbreadths below the right costal margin.

The extremities, as stated before, showed the fingers and toes to be long and slender, with lengthening of the phalanges. There was no clubbing, webbing, cyanosis, or thickening of the joints. The feet were long, slender, and flat (5.5 inches long). There was slight pronation, knock knees, and long slightly bowed tibias and femurs. There was no marked hyperextensibility, and neurological examination was negative.

Laboratory studies were negative. Chest roentgenography showed a slight prominence of bronchovascular markings at both hilar regions. Diaphragm, ribs, trachea, and heart were normal. A skeletal survey showed no abnormality in the skull, spine, hands, feet, or pelvis. The osseous age was compatible with the chronological age. Electrocardiography showed a right axis deviation, which was interpreted as not unusual for a child of this age.

DISCUSSION

Marfan's original description of arachnodactyly in 1896 did not mention the characteristic ocular defects that now have become an integral part of the syndrome that bears his name. In 1922 Achard[3] first noted the familial incidence. Cardiovascular anomalies were first described by Salle in 1912. Boerger in 1913 described a child with arachnodactyly, heart failure, kyphosis, and congenital luxation of lenses; at autopsy the child was found to have a patent foramen ovale and abnormal lobulations of the lungs. It remained for Ormond and Williams[4] in 1924 to stress the striking ocular findings. Frequent mention of the syndrome has been made recently in ophthalmological literature, since approximately 80 per cent of cases show ocular defects. In fact, the diagnosis of Marfan's syndrome has come to be accepted as unequivocal with the identification of arachnodactyly and ectopia lentis.

The cardiovascular anomalies are found in approximately 40 to 60 per cent. Much attention has been directed to these in recent reports, and the indication is that, with continued identification and study, this percentage will rise sharply. From a clinical standpoint the cardiovascular anomalies are particularly significant formes frustes.

Black and Landay,[5] in a recent description

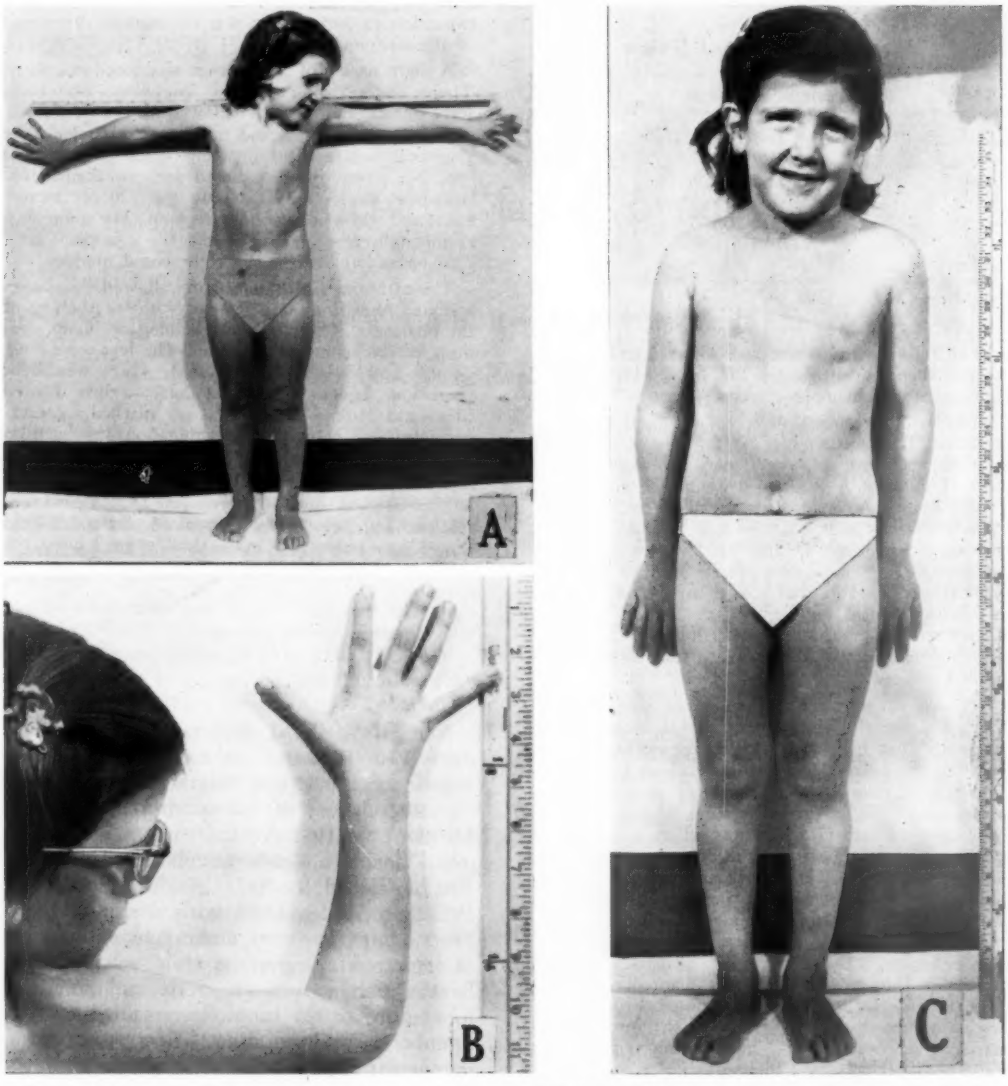

Fig. 1 (A) Patient at 3½ years showing long, slender phalanges. Height 41.5 inches; span, 41.5 inches. (B) Thick-lensed glasses and facial configuration give patient an unusual, wizened, elderly appearance. Note dolichocephaly and slender, graceful fingers. (C) Patient showing frontal bossing, prominent auricles, narrow jaw angle, and malocclusion.

of a family in which 5 cases of Marfan's syndrome occurred, point out that more emphasis should be placed on the recognition of this entity, in order to stress the hereditary aspects and "the advisability of not bringing too many children so affected into the world." It is probably of some significance that with modern therapy more of these patients will live to childbearing age and thus swell the number of cases that are appearing.

A difference of opinion exists on the hereditary aspects of the disease. Rados[6] did not agree that the single gene theory was responsible for the multiple defects. He suggested instead a series of linearly arranged genes, each of which might be responsible for some facet

of the syndrome. Another theory[7] is that a "simply dominant autosomal phenotropic factor, the effects of which are sensitive to modification by other inherited genetic modifiers and perhaps factors in the early environment," is responsible for the wide variation of the inheritance pattern. The authors hold that this theory accounts for the difference between the full-blown case and the forme fruste. In addition, McKusick[8] states that his data indicate that approximately 15 per cent of all cases occur as a result of *de novo* mutation.

Lutman and Neel[7] examined 27 members of a kinship of 40, 17 of whom were thought to exhibit Marfan's syndrome. Marriages between normal and affected individuals produced 14 normal offspring and 16 demonstrating Marfan's syndrome or a forme fruste. Five of the 16 had the triad of arachnodactyly, ectopia lentis, and cardiac anomalies; 9 had two of these defects, while 2 had only ectopia lentis. Five individuals in the so-called normal group of 14 offspring died young; data were insufficient to prove or disprove a diagnosis. This study emphasizes the value of a detailed family history when finding the isolated components of the syndrome. In fact, a true diagnosis of a forme fruste might be available only after a careful evaluation of this kinship.

Numerous theories have been advanced regarding the etiology of Marfan's syndrome: toxinfectious origin, disorders akin to those causing muscular dystrophy, endocrine disturbance particularly involving pituitary imbalance, nervous origin, dysrhaphia, degenerative anomalies, and embryologic alteration. At present, the consensus is that the disease is due to a congenital defect in connective tissue. Recent work of Ponseti[9] and Shepard suggests a hereditary defect in chondroitin sulfate metabolism. Another recent theory ascribes the defect to an abnormality of the endocrine system, causing disturbance in the ground substance.[10] Some authors have suggested that the defect of connective tissue causing the cardiovascular anomalies lies in the elastic fibers and may be the same underlying cause responsible for Erdheim's cystic medial necrosis in dissecting aneurysm.

Marfan was first attracted by the long delicate "spider-like fingers and toes." The clinical picture is more extensive now. There is a relative and absolute increase in the length of the hands and feet, especially the metacarpals, metatarsals, and phalanges. This tendency to increased length is seen in all the long bones, especially at the distal ends. Roentgenograms show less slenderness and rarefaction than expected, the frail appearance being due to scantiness of subcutaneous fat and poor muscular development of the entire body. Other skeletal, muscular, and ligamentous features seen are webbed toes and fingers, hernias, hammer toes, club feet, and knock knees. Dolichocephaly is seen in approximately 80 per cent of these cases. The characteristic facies are produced by prominent supraorbital ridges, frontal bosses, a high arched palate, protruding front teeth, and prognathism. Dorsal kyphosis, scoliosis, and pigeon breast are also commonly seen. Poor muscular development, especially of the extremities, and increased mobility of joints due to lax ligaments are frequently found. Large flaccid ear lobes with a deficiency of cartilage of the pinna and overdevelopment of the crus helices are a manifestation of this disease.

The eye defect most commonly seen is bilateral ectopic lenses. It is usually accompanied by many or all of the following elements: a high degree of myopia, miosis, iridodonesis, global hypotonia, detachment of the retina, divergent squint, complete amblyopia, megalocornea, lens defects, and edema of eyelids. In one study of 7 cases of ectopia lentis, the displacement was upward. Colobomas, when present, were on the lower peripheral part of the lenses. A possibility of nearly normal, or at least relatively stronger, superior zonular fibers is suggested for the upward displacement of the lens, the greatest disturbance occurring in the embryologically less stable inferior region corresponding to the fetal cleft.[7]

The principal cardiovascular anomaly seen in Marfan's disease is involvement of the aorta. Other defects are patent interatrial septum, coarctation of the aorta, dysrhythmia, conduction defects, and rarely pulmonary artery lesions. McKusick,[8] in his study of 50 kinships, states that the defect is an abiotrophy, the involved tissues wearing out prematurely under stresses and strains. He points out that the microscopic description of the aortic lesions in his study are compatible with Erdheim's cystic medial necrosis, i.e., a rarefaction of the media with derangement of elastic lamellae and with cystic spaces separating the irregularly arranged muscle bundles. Clinically these changes produce dilatation of the ascending aorta, which in turn usually results in a profound aortic regurgitation. The localization of the aortic lesion to the preinnominate portion is

due to the arterial pressure being maximal at this site and is characteristic of both Marfan's syndrome and syphilis. In the differential diagnosis between Marfan's disease and syphilis, rheumatic heart disease, bacterial endocarditis, and traumatic rupture of an aortic cusp, the associated anomalies and family history are significant factors. In the presence of the Flint murmur of aortic regurgitation and a prominent pulmonary conus without any associated anomalies or any other proved diagnosis, the review of family history and physical findings in the kinships are especially important. Any of the afore-mentioned diseases might be superimposed on Marfan's syndrome with dire and immediate results.

Dissecting aneurysm in the aorta may result from the same cause as aortic dilatation. The common site is in the thoracic aorta. However, a dissecting aneurysm was found in a 55 year old white World War II veteran with arachnodactyly[11] in which the defect extended the entire length of the aorta and down the left iliac artery to its bifurcation.

In a recent series of 55 post-mortem examinations of the full-blown disease,[12] the following distribution was found: 22 aortic lesions, 21 endocardial lesions, 13 combined aortic and endocardial lesions, 9 septal defects, and 1 dilated and 1 normal heart. In 3 cases of Marfan's syndrome with aneurysmal dilation of aortic sinuses recently reported,[1] the diagnosis was made by angiocardiography. Two of these patients were asymptomatic and all were living in 1955. Knowledge of the scope of the syndrome and a high index of suspicion are to the credit of the physician.

SUMMARY

A classical example of Marfan's syndrome has been presented and discussed. The patient is the sixth child in a family of 7 children. The maternal grandmother was reluctant to give information about the family history, and little knowledge of the kinships was available. One maternal aunt is quite slender and taller than her siblings, but exhibits no other suggestive characteristics. The mother has hammer toes and webbing of her first two toes. Three female siblings exhibit syndactylia bilaterally and 1 of them has an umbilical hernia. One of the male siblings had bilateral inguinal hernias. An umbilical hernia developed at a later period. So far no one has shown cardiovascular disease, although this may develop at a later date. The hereditary pattern of this disease is well shown in this interesting family group.

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Medical Highlights

TAG TECHNIQUE SPEEDS DIAGNOSIS OF INFECTION

A new laboratory technique, expected to save thousands of lives through permitting earlier diagnosis and specific treatment of a whole series of infectious disease entities, was described in an interview with *Scope Weekly* by Dr. Alan W. Donaldson, Assistant Chief of the U. S. Communicable Disease Center in Atlanta, Ga.

The new technique, developed as a counter to biologic warfare but with expanding peacetime values, uses a fluorescent dye to tag serum antibodies. These antibodies, each a specific against a given pathogen, have been and are being developed in animals in the Government laboratory against a growing range of pathogens.

If a drop of tagged antibody solution is placed on a smear of suspected material containing the pathogen to which it is related, the organism glows with a greenish light when placed under a microscope equipped with ultraviolet light. A battery of these identifying tests with tagged antibodies developed against specific pathogens can be swiftly run through. Identification may be done within an hour or less as contrasted to the 48 or 72 hours or even the week sometimes necessary to get pure cultures in the standard laboratory methods.

Seldom do cold-war activities pay off in terms of notable peacetime advance but the fluorescein-tagged antibody technique involves such a case, Dr. Donaldson said. Not only will the method permit the rapid identification of purposely placed pathogens in any possible war, when older methods might have resulted in the death of thousands, but, Dr. Donaldson believes, it will also open up a whole new chapter in epidemiology. Above all, he says, it will ultimately permit doctors everywhere to institute an almost immediate specific therapy for infectious diseases of uncertain initial cause.

"We got started in this," he says, "as part of our civil defense activities and so we worked first on potential biological warfare agents, trying to determine how to identify them not in a matter of days or a week but at once. Thousands might die if identification were done under the conventional methods. We succeeded in developing antibodies for identifying pathogens which cause brucellosis, salmonellosis, plague, tularemia, anthrax, and melioidosis.

"Since then we have broadened its application to streptococcal infections and also viruses, and we can identify and type polio, encephalitis, and influenza viruses. We can use the method to rapidly detect bacterial agents in exudates and transudates such as pus, sputum, nose and throat smears, where the specimens are often contaminated and where other laboratory techniques don't work at all. We are making marked progress in producing specific tagged antibodies for the detection of serotypes of streptococci and leptospirae and for the organisms which cause meningitis, tuberculosis and diphtheria.

"The new method will help our fight against encephalitis and almost every other disease with which we are concerned. I think it's one of the best things we have ever done at CDC, an outstanding advance in laboratory diagnostic work which will have lasting results in the actual clinical treatment of disease by permitting specific therapy to be instituted much more promptly."

In speaking of the actual technique, Dr. Donaldson said, "The only time an antibody combines with a bacterium is when there is a relationship between the two, so we develop antibodies for each of the bacteria we want to identify. Suppose we are interested in plague, we will immunize rabbits against plague by infecting them with plague organisms. They will develop a serum antibody against plague. If we take that serum, as we have, and tag it with this fluorescein dye, we can use it to identify plague. It's almost like putting a neon light on these organisms.

"Essentially the technique consists of (a) spreading material suspected of containing a given pathogenic organism on a slide, (b) covering the smear with a drop of known antibody solution which has previously been tagged with fluorescein, (c) washing to remove excess antibody solution, and (d) examination of the smear under ultraviolet light by means of a microscope provided with special optical equipment."

Dr. Donaldson warned, however, that physicians might not be able to use the faster diag

nostic methods for a year or more. In the first place fluorescein compounds satisfactory in producing tagged antibodies are just beginning to be commercially produced. In the second place not many state and county public health laboratories are equipped with ultraviolet lighting.

In addition, Dr. Donaldson pointed out that the new procedure, as is true of most of the conventional techniques, is restricted to the identification of bacteria in which specific antigen-antibody reactions can be demonstrated and that further developmental studies are necessary to fully evaluate its usefulness.

The first use of fluorescein in tagging antibodies was at Harvard in 1942, but then it was used entirely as an investigatory procedure in tracing physiologic processes. The first diagnostic use was at the Communicable Disease Center in 1954 when the Center began its search for better methods to combat possible biologic warfare.

Dr. Morris Goldman did the preliminary research on parasitic organisms. Drs. Max Moody and William B. Cherry directed the investigation of bacteria and Drs. Charles Shephard and Robert Goldwasser have conducted the phase of the problem concerning viruses. (Reprinted from *Scope Weekly*, courtesy of The Upjohn Company, Kalamazoo, Mich.)

RADIOACTIVITY FOR DRUGS, FOOD, AND PLANTS

Dr. Henry Seligman of the Atomic Energy Research Establishment at Harwell asked a meeting of more than 1,000 scientists from 50 countries, gathered in Paris by UNESCO for the International Conference on Radioisotopes in Scientific Research, to follow him in a survey of the exciting development of isotopes and radiation energy.

Dr. Seligman described applications in many industrial processes: irradiating polyethylene, for instance, gives it far superior high temperature properties, so that it can be used for tubes and cheap electrical cables. Radiation may also be used in the vulcanization of rubber; it improves the performance of transistors in digital computers and it helps to produce plastics at ordinary pressures and temperatures, instead of the costly high-pressure process.

But opportunities look even greater for the industrial use of radiation in sterilization procedures. Provided that a sufficiently large dose is given, radiation can kill most forms of living organisms. Doses of this order, says Dr. Seligman, can be easily administered to drugs and it can be shown that the total chemical change in the drug produced by this radiation is almost negligible. A further advantage is that the delivery of a dose of this magnitude to a drug results in a rise in temperature of only 1 or 2 C. Hence any damage to the product which might occur on heating is entirely eliminated. Already it has been shown that antibiotics such as penicillin, streptomycin, aureomycin, and terramycin can be sterilized by radiation without any loss of potency. This work has been extended to the sterilization of surgical dressings and even to bone and artery sections for grafting.

Hypodermic needles can, of course, be sterilized by heat and then subsequently packed in sterile plastic envelopes. However, the reliability of the sterility is improved if the sterilization process is performed after the hypodermic needle has been sealed in its container. Packaging of this kind is of special merit in emergency packs which may have to be used under conditions where there is no sterilizing equipment. The same sort of considerations apply to burn dressings and sutures, but with the additional justifications that some burn dressings are heat sensitive and that the strength of some sutures may be reduced by heat sterilization.

When hospital bedding is laundered, it is still far from being free from spores and bacteria, which can cause infection. In particular, the bedding from surgical wards often requires treatment in a steam autoclave. Unfortunately woolen blankets may be ruined by two or three treatments in an autoclave, and so an unhappy compromise is usually struck between economy and reinfection. Blankets can be sterilized by irradiation without an appreciable rise in temperature, and, although there is some slight damage to the fibers, an average blanket can survive as many as 20 sterilizations by radiation.

There are many ways in which atomic radiation may be used to help in the preservation of food. Perhaps the simplest of these, and one requiring a small dose, is the prevention of sprouting of potatoes. The lowest doses appear to delay the sprouting only and are being considered as a means of extending the marketing areas of seed potatoes to such places as South Africa and Australia. A slightly larger dose will prevent sprouting of potatoes harvested

late in summer until the following summer or even later. (UNESCO)

FEMALE SEX HORMONE SHOWS PARADOXICAL EFFECTS IN MALES

Progesterone acts as a chemical castrating agent when given to normal men, and similar synthetic hormones (progestagens) have the same effect. This information was presented in late 1957 at a New York Academy of Sciences conference on "New Steroid Compounds with Progestational Activity" by investigators representing the University of Oregon Medical School and the Rockefeller Institute for Medical Research. Parke, Davis and Company, G. D. Searle and Company, and E. R. Squibb and Sons were co-sponsors.

Administration of the synthetic hormones and of the natural progesterone caused a quick drop to zero in the sperm counts of 20 normal male prisoners in Oregon State Penitentiary who volunteered for the experiments. As the sperm counts fell, other attributes of masculinity, including interest in sexual experience, also fell, reported Dr. Carl G. Heller. This was as true for homosexual prisoners as for those of normal attitude. When administration of the hormone and its synthetic "cousins" was stopped, there was a quick resurgence of masculine characteristics and a sharp rise in the sperm count. As of Oct. 4, when the last test was made, all the 20 test subjects had sperm counts higher than before the experiment was begun.

Endocrinologists at the meeting, who commented on the Oregon experiment, suggested that it might point the way to a useful treatment for male infertility, when that is due to low sperm count. The question was also raised whether the new hormonal substances might be employed to supplement psychological treatment of homosexuality.

CALORIC RECOMMENDATIONS

Part of the fourth annual Graduate Symposium on Geriatric Medicine, co-sponsored by The American Geriatrics Society and The American Academy of General Practice and made possible by a grant from Schering Corporation, was devoted to a panel discussion of "Clinical Nutrition and Lipid Metabolism." Several hundred doctors attending the symposium, held in November, 1957, were told that the average man of 25 years of age requires only 2,800 calories a day to maintain his body weight and supply the necessary energy.

According to Herbert Pollack, M.D., Associate Professor of Clinical Medicine, New York University Post-Graduate Medical School, and Associate Physician for Metabolic Diseases, Mount Sinai Hospital, a person should decrease his caloric intake by 10 per cent each decade, 1 per cent a year, to prevent gaining weight. A man of 20 years can expect to gain about 50 pounds by the time he reaches 60 if he continues to consume the same number of calories without a regular decrease. Dr. Pollack said that his recommendations are for a re-evaluation of former, higher caloric recommendations.

The common use of mineral oil with meals, as in salad dressings, was criticized by several of the panel members who pointed out that oil soluble vitamins such as vitamins A, K, and E dissolve in the mineral oil and are excreted. In a salad, the mineral oil tends to prevent assimilation of vitamins by the body. The doctors said that if mineral oil is used it should be taken at bed time and not with meals.

CARE OF MENTAL PATIENTS

The general practitioner is the first line of defense against the ravages of mental illness, since the patient sees him first, a Baltimore psychiatrist told a meeting of general practitioners in Baltimore on Dec. 12. Therefore, reasoned Dr. Frank J. Ayd, Jr., the family doctor should be "indoctrinated in the art," of recognizing the early manifestations of an emotional ailment. He should be able to "detect those patients who should be referred for specialized treatment and those he can properly manage."

The general practitioner must be more than an able diagnostician, Dr. Ayd said. He must also have a "thorough, practical knowledge" of drugs used to treat psychiatric patients. Each has specific indications, contraindications, and side effects, he declared, adding that some are more suitable for psychotics, while others only help neurotics. "A doctor is well advised to become acquainted with a few tranquilizers rather than with all of them so he can use them advantageously and with the least risk." However, the psychiatrist warned, "drugs do not replace patient-physician relations nor any of the previously accepted techniques of psychiatric treatment."

President's Message

REVISION OF THE CONSTITUTION AND BY-LAWS: PROGRESS REPORT

The members of the Constitution and By-Laws Committee were very pleased by the response of the officers and the members of the Association when the proposed new Constitution and By-Laws was read at the Midyear Meeting in Dallas. They appreciated the helpful and constructive suggestions that reflected not only personal study but also prior discussions they had held at branch meetings and with other members. On the other hand, comments received by mail have not been abundant.

Your Consitution and By-Laws Committee feels strongly that in a matter of such importance every member should be given ample time to express her opinions. For this reason the Committee recommends that voting should be deferred until after the Annual Meeting in June of 1958. They further suggest that the vote should be taken by a mail ballot of the entire membership at a later date. In order to provide a mail ballot it is necessary to revise Article VII of the Constitution and Article IX of the By-Laws now in effect. Action must be taken at the 1958 Annual Meeting to revise these articles.

Meanwhile all members who are interested are urged to write directly to the Chairman of the Committee, Josephine Renshaw, M.D., 1150 Connecticut Ave., Washington, D. C. The JOURNAL may be used for editorials on the subject. It is urgent that each member watch the JOURNAL closely for the revisions and editorials.

The following resolutions will be presented for action at the Annual Meeting in June, 1958:

Whereas, our present Constitutions and By-Laws can be amended only at an Annual Meeting, and

Whereas, from time to time there are issues of such importance that each and every member should have the privilege of voting for or against such issues,

Be it therefore resolved that Article VII of the Constitution and Article IX of the By-Laws be amended to read respectively:

This Constitution may be amended at any Annual Meeting by a three-fourths vote of the paid-up voting members present, or by a three-fourths vote of returned mail ballots, all paid-up active members having been sent a ballot, provided the amendment shall have been given the members either by mail or by publication in the official organ of the Association at least 30 days before the amendment is presented for vote.

The By-Laws may be amended at any regular meeting by a majority vote of the paid-up voting members present, or by a majority vote of returned mail ballots, all paid-up active members having been sent a ballot, provided the amendment shall have been given the members either by mail or by publication in the official organ of the Association at least 30 days before the amendment is presented for vote.

Whereas, providing a mail ballot for each member will necessitate financial expenditure, and

Whereas, such item is not included in the 1958 budget,

Be it therefore resolved that this assembly authorize the treasurer to disburse the necessary funds to cover the cost of this mailing.

Elizabeth S. Kahler

New Honor for Helen Johnston, M.D.

Dr. Helen Johnston of Des Moines, Iowa, was chosen by the Delta Zeta sorority as the 1957 Woman of the Year. The selection was made by Delta Zeta judges from Illinois, Texas, and New York. Dr. Johnston was honored by the Iowa Delta Zetas at a tea in the Gamma Epsilon chapter house at Drake University, where the lovely Delta Zeta Woman of the Year silver medal was presented to her.

Dr. Johnston received her B.S. degree from Drake University in Des Moines in 1913 and was named a member of Mortar Board. Her first two years of medical training were received at the University of Iowa from 1915 to 1917. She received her M.D. degree from Cornell University College of Medicine in New York City in 1919 and interned at Memorial Hospital, Worcester, Mass., from 1919 to 1920. Since 1920 she has been a physician in Des Moines with a specialty in internal medicine.

The award committee summarized their decision in this way: "For first place, Dr. Helen Johnston. Her amazing scope has brought her international, national, state, and local acclaim. A woman of great generosity and skill, she has literally sown her life into the furrow of the world's great need."

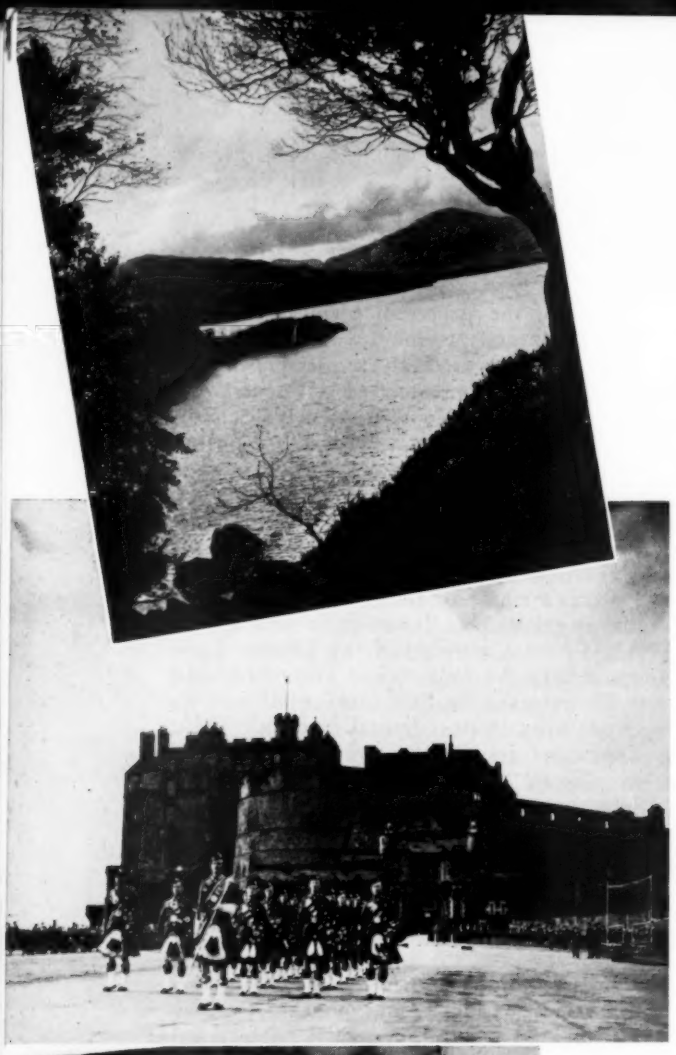
Dr. Johnston served her sorority as treasurer from 1928 through 1936 and has continued her devotion and service to the sorority throughout the years. She served two terms as president of Altrusa International in 1928 and 1929. Through her membership in PEO Sisterhood (Iowa Association), Des Moines Professional Women's League, American Association of University Women, Business and Professional Women's Club, the Des Moines Woman's Club, the Des Moines Chamber of Commerce, and the Embassy Club, Dr. Johnston is known to many persons outside of the medical profession.

The medical profession has honored Dr. Johnston in many ways. She has been listed in "Who's Who in Medicine," "Who's Who in America," and "Who's Who in the Midwest." In 1956, Dr. Johnston was named Medical Woman of the Year by the Iowa Branch of the American Medical Women's Association and presented with a citation by the AMWA at the Midyear Meeting in Boston. Dr. Johnston served AMWA as president in 1946-1947. In 1934 she was a delegate to the Medical Women's International Association meeting in Stockholm, Sweden, and in 1947 and 1952 she served AMWA as councilor at the meetings held in Amsterdam, Holland, and in Vichy, France. She plans to attend the MWIA General Assembly in London, in July, 1958, as a councilor for the AMWA. At the present time Dr. Johnston is serving the AMWA as a member of the Finance Committee and the Publications Committee. She is a member of the Polk County Medical Society, Iowa State Medical Society, AMA, American Geriatrics Society, and AMWA and its affiliate, the Iowa Branch. In 1954 Dr. Johnston was chosen by Charles E. Wilson, then Secretary of Defense, to serve for a four year term on the Women's Defense Advisory Committee on Women in the Services. This important committee of 50 outstanding women of the country meets at the Pentagon twice each year.

Friends marvel at her stamina in meeting the many demands made upon her time by patients and by her diversified hobbies and activities. She is an avid fisherman, enjoying this sport in recent years in the Gulf of Mexico and Canadian and Minnesota waters. Other interests are travel and gardening. She is also active in the operation of the Johnston family farm of 700 acres, which has been owned by her family for more than 100 years.

Not only because of her professional achievements but also because of her unfailing loyalty to Delta Zeta throughout the years, the Des Moines alumnae chapter and the collegiate chapters at the University of Iowa, Drake University, and Iowa State College felt that no more deserving member could be presented for this top honor for alumnae of Delta Zeta.

The AMWA extends congratulations to Dr. Johnston for this merited honor and to Delta Zeta for their wise choice of Dr. Johnston as the 1957 Woman of the Year.



(Upper) Killarney. *(Middle)* Edinburgh. *(Lower)* Stratford.

1958 MWIA 1958

The tour to Europe offered in connection with the MWIA's Eighth Congress in London is a project in which sightseeing, professional programs, and relaxation are extremely well balanced.

Dublin, Belfast, Edinburgh, London, Stratford-on-Avon, Bruges, and Brussels with its World Fair; Paris, Chartres, and the Loire country; Barcelona and Madrid; the fabulous cities of Andalusia, Córdoba, Granada, Málaga, Algeciras, and Sevilla; and Lisbon are some of the exciting highlights of the sight-seeing program.

Visits to the famous maternity hospital (Rotunda) in Dublin; to Edinburgh University and the Royal Free Hospital; to the Sorbonne, Pasteur Institute, and St. Louis Hospital in Paris; to various institutions in Barcelona; to the University and Institute of Spanish Culture in Madrid; and to the Instituto Portuguese de Oncologia in Lisbon will comprise the professional program, besides, of course, the Congress program in London and social meetings with local medical women everywhere.

The beautiful Irish countryside with Killarney, Glengaridd, Cashel and Blarney castles, and Glendalough; the Scottish Highlands with Loch Lomond and Loch Ness, Oban and the mysterious island of Iona, the Stones of Clava, Balmoral, Braemar, St. Andrews, the Firth of Forth, and the Trossachs; the Lake District, the Welsh mountains and coast, Stonehenge, Biarritz, the Basque countries and the Pyrenees, Malorca and the plains of Castile, with Toledo, Segovia, Avila and the Escorial, and finally the sandy beach of Estoril—all these will afford the maximum of recreation in unique surroundings.

INTERNATIONAL TOUR

Performances at the famous Abbey Theater in Dublin, the Shakespeare Memorial Theater in Stratford, and the Opera and Folies Bergeres in Paris, and the optional attendance of a bullfight in Spain, will provide some of the additional entertainment.

The entire Tour, leaving New York June 26, 1958, and returning Aug. 24, will cost $1,945. Those unable to participate in the full tour will have the following choices:

Pre-Congress. Part I: From New York June 26 to Eire, North Ireland, Scotland, Wales, and England, ending July 15 upon arrival in London. The cost of Part I, New York to New York, is $995, all inclusive. Part II: The stay in London during the MWIA Congress, July 15 to 21, is not included in the Tour price, since these arrangements are being made by the MWIA.

Post-Congress. Part III: July 22 to 30, to Bruges, Brussels and the World Fair, and Paris. Part IV: July 30 to Aug. 24, to the Basque Country, Spain, and Portugal. Together these cost $1,495. Part III is optional since some members may wish to take part in the post-Congress tours in the British Isles being arranged by the MWIA; a refund of $100 will be granted members omitting this part and joining Part IV in Paris after staying over in England at their own expense. Members who must return earlier may leave the group in London, Paris, or Madrid, returning directly to New York by plane, and proportionate refunds will be granted. Extensions may be arranged according to individual desires and also trans-Atlantic transportation by ship for those who prefer this. Friends and relatives, male and female, are invited to join the Tour. For further details, write immediately to Dr. Ada Chree Reid, 118 Riverside Drive, New York 24, N.Y.

(Upper) Paris. *(Middle)* Amboise Castle, France. *(Lower)* Madrid.

Opportunities for Women in Medicine

AWARDS

Medical Student. The 1958 Schering award, open to medical students in the United States and Canada, is designed to encourage interest and activity in the vital field of medical communications. In addition to first and second prizes of $1,000 and $500 in each of three categories, nine new cash awards will be made to the third, fourth, and fifth best manuscripts in each field. A total of $5,700 in cash prizes, plus many honorable mention prizes will be awarded.

Three important medical subjects have been selected as topics for this year's contest. These are: "The Mechanism and Current Concepts of Treatment of Nausea and Vomiting," "Current Trends in Corticosteroid Therapy in Pediatrics," and "The Uses of Tranquilizer Therapy in Office Practice." All medical students in accredited medical colleges are eligible to participate. Entry blanks and contest rules are available in all medical schools.

Medical Writing. The Mississippi Valley Medical Society has announced its annual essay contest. Any subject of general medical or surgical interest may be discussed, provided the paper is unpublished and of interest and value to general practitioners. Contributors must be members of the AMA and residents and citizens of the United States. Manuscripts must not exceed 5,000 words and five complete copies must be submitted. The winner will receive $100, a gold medal, a certificate, and an invitation to read the essay at the annual meeting of the Society on September 24-26, 1958, in Chicago.

CAMP PHYSICIAN

Established Vermont girls' camp, July and August, or either—$900 for full season. Write Herbert Brill, 60 Remsen St., Brooklyn 1, N.Y.

COURSES

Fractures and Trauma. The second annual postgraduate course in Fractures and Other Trauma will be given by the Chicago Committee on Trauma of the American College of Surgeons for four days from April 16 through April 19 at the John B. Murphy Memorial Auditorium, 40 E. Erie St., Chicago. Topics will include trauma of the hand, head, chest, abdomen, heart, knee, and shoulder; treatment of burns; athletic injuries; and other subjects selected in answer to a questionnaire sent to last year's registrants. Illustrated lectures, patient demonstrations, and question and answer periods will also be held.

Registration fee is $50.00. Residents, interns, and students will be admitted free if a note of identification from chief of service or dean is provided. All inquiries may be addressed to Dr. John J. Fahey, Chairman, 1791 W. Howard St., Chicago 26.

Oral Pathology. A course in Advanced Oral Pathology will be presented from April 28 through May 2 at the University of Minnesota by medical and dental staff. Tuition is $50, and an additional $50 will be charged if room and board are desired. For further information, write to Dr. Robert J. Gorlin, Chairman, Division of Oral Pathology, School of Dentistry, University of Minnesota, Minneapolis 1.

EXAMINATIONS

Foreign Students. The American Board of Anesthesiology at its October, 1957, meeting voted to accept the examination of the Educational Council for Foreign Medical Graduates as meeting its requirements for medical school graduation for those physicians who graduated from medical schools outside the United States and Canada.

The first American Medical Qualification examination will be given in something like 50 medical schools in this country for foreign medical graduates who are already over here. It will be given sometime, for one day, during the months of February or March, 1958. The next American Medical Qualification examination will be given in 15 to 30 foreign stations as well as in the 50 American stations, and its dates are one day in the months of July or

August, 1958. Before the applicant can take these examinations, he must have his credentials submitted and approved at the ECFMG.

Those interested in applying for this American Medical Qualification examination should write immediately to Dr. Dean F. Smiley, Executive Director, Educational Council for Foreign Medical Graduates, 1710 Orrington Ave., Evanston, Ill., for further information.

It will not be possible for those who pass the ECFMG exam to be cleared in time for the July, 1958, written examination of the American Board of Anesthesiology, but it is expected that they will be able to apply for the July, 1959, examination.

MEETINGS

Gynecology and Obstetrics. The Second World Congress of the International Federation of Gynaecology and Obstetrics will take place in the Queen Elizabeth Hotel in Montreal, Canada, June 22 to 28, 1958. Round-table conferences will be held separately in gynecology and in obstetrics. The subjects in gynecology are as follows: (1) The Limits of Pelvic Surgery in the Treatment of Carcinoma of the Cervix, (2) The Correlation of Psychosomatic Medicine in the Ovarian Function, (3) The Diagnosis of Carcinoma of the Cervix, and (4) Genital Tuberculosis. The following subjects in obstetrics will be discussed: (1) Psycho-Prophylatic Preparation to Labour, (2) Physiology and Pathology of the Contraction of the Human Gravid Uterus, (3) Anemia of Pregnancy, and (4) Toxemias of Pregnancy.

All correspondence should be addressed to the Montreal Committee, Second World Congress, International Federation of Gynaecology and Obstetrics, 1414 Drummond St., Suite 220, Montreal 25, Quebec, Canada.

Internal Medicine. The Fifth International Congress of Internal Medicine will convene in Philadelphia on April 23-26, 1958. Those who wish to become members of the International Society of Internal Medicine and who would like to attend the Congress should request application forms from Mr. E. R. Loveland, Secretary-General, Fifth Congress, 4200 Pine St., Philadelphia 4.

Pan-American. The VI Congress of the Pan-American Medical Women's Alliance will be held in Miami, Fla., April 14-17, 1958. Headquarters will be the Hotel McAllister. Women physicians of the United States and Canada are cordially invited to become members and attend the Congresses that are held every two years alternately in North and South America. Delegates are expected to represent the medical women of most of the Latin-American Republics. The scientific program is translated into both languages and deals with medical problems of mutual interest.

Two post-Congress trips are being planned. One is to the Carribean area where some of the member groups will be visited. The other is to Washington, D. C., where the hospitality of the Pan-American Union and the various Latin- American organizations is being offered. The Latin American Music Festival also is being held in Washington at this time. Further information can be obtained from Hilla Sheriff, M.D., Publicity Chairman, Division of Maternal and Child Health, South Carolina State Board of Health, Columbia 1.

TRAINING GRANTS

Public Health Service. A new program to increase the number of trained scientists for research and academic careers in fields of basic importance to health has been announced by the Public Health Service. Designed to provide aid for graduate level training in medical schools, universities, and other qualified training institutions, the new program is to be financed through the Service's National Institutes of Health and will be known as the "General Research Training Grants Program."

"Additional trained research personnel are badly needed," said Dr. James A. Shannon, Director of the Institutes, "in such shortage areas as pathology, pharmacology, genetics, anesthesiology, epidemiology, biometry, biochemistry, biophysics, and others from which will come new basic knowledge vital to the conquest of disease. This new program of grants to institutions extends and supplements, but does not replace, the research training opportunities that are available through our regular research fellowship awards to promising individuals."

The program is financed through funds appropriated by Congress to the Institutes for training grants during the current fiscal year. Existing funds will be used to focus aid upon training in the basic sciences where there are major shortages of research personnel.

Institutions receiving funds under the new program will select and appoint individuals for predoctoral and postdoctoral training. The institutions will determine stipends to be paid. They are not restricted to a set pattern in developing training but may propose programs of any nature that reflect research training needs as seen by the institutions and that provide the best utilization of their facilities.

The General Research Training Grants Program will be administered by the Division of Research Grants of the National Institutes of Health. Institutions wishing further information, including application forms and instructions, may obtain them by writing to the Chief, Research Training Branch, Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

TRAINING PROGRAM

Steroid Research. The Worcester Foundation for Experimental Biology, Shrewsbury, Mass., the Department of Chemistry, Clark University, Worcester, Mass., and the Department of Biochemistry, College of Medicine, University of Utah, Salt Lake City, have announced the Third Training Program for Steroid Biochemistry, starting Oct. 1, 1958. This program is offered by the U.S. Public Health Service through the National Cancer Institute of the National Institutes of Health. The courses stress both theoretical and practical aspects in steroid research and offer training in specialized laboratory techniques.

Postdoctoral candidates (M.D. or Ph.D) selected for admission will receive stipends of $5,000 for a one year period. Predoctoral candidates (B.S., M.S., or equivalent) selected for admission will receive stipends of $1,500 for a six month period.

The final date for application is June 1, 1958. Send inquiries and applications to: Dr. Kristen Eik-Nes, Department of Biochemistry, College of Medicine, University of Utah, Salt Lake City, Utah, or to Training Program for Steroid Biochemistry, Department of Chemistry, Clark University, Worcester, Mass.

THESE WERE THE FIRST

DR. GERALDINE CROCKER, graduate of the University of Michigan Medical School in 1924, was the first woman physician in Licking County, Ohio, and first to be examining physician of the Columbus Young Women's Christian Association.

DR. JENNIE A. GREEN, born in 1858, graduated in 1890 from the Woman's Medical College, Northwestern University, was the first woman to practice in Coles County, Ill., and was the first woman admitted to the Presbyterian Hospital, Chicago.

DR. MATTIE H. GRUBEN graduated in 1947 from the Woman's Medical College of Pennsylvania and was appointed chief resident physician at The California Hospital, Los Angeles, the first time a woman physician was accorded this position.

DR. GIOCONDA RITA SARANIERO graduated in 1935 from the Woman's Medical College of Pennsylvania and entered the U.S. Navy in 1943, serving overseas since June, 1954. In November, 1955, Dr. Saraniero became the first woman captain in the Medical Corps of the U.S. Navy in Naples, Italy.

DR. IDA MAY SHIVELY, born in 1868 near Osceola, Iowa, was the first woman to receive a B.S. degree from Battle Creek College (1892). In 1897 she graduated from the Woman's Medical College, Northwestern University. Dr. Shively practiced first in Cleveland and then in Colorado, retiring in 1940.

DR. BERTHA V. THOMSON of Peru, Neb., a graduate of Woman's Medical College, Northwestern University, was the first woman to be city physician in the state of Wisconsin and one of the first women physicians on the staff of Winnebago State Hospital. Dr. Thomson served for 12 years as a medical missionary in India.

—From the ELIZABETH BASS Collection,
Rudolph Matas Medical Library,
Tulane University, New Orleans.

News of Women in Medicine

DR. KATHERINE BAIN, Assistant to the Chief of the Children's Bureau, served as chairman the week of Oct. 21 of a conference on the use of roentgen-rays as a diagnostic tool in the care of children and pregnant women. Mrs. Katherine Brownell Oettinger, Chief of the Bureau, said that the Bureau has interest in the roentgen-ray problem because of its program of service to crippled children and its interest in maternal and child health.

DR. JEANNE C. BATEMAN presented a paper entitled "Role of Marsilid in the Care of Far Advanced Cancer" at the Symposium on Marsilid held at the Barbizon Plaza Hotel in New York on Nov. 29 and 30. The symposium was sponsored by Hoffman-La Roche, Inc., and included not only biochemical and animal studies but also clinical observations on the use of this agent in hypertension, depressive states, angina pectoris, and other disease states.

DR. VIOLA BERNARD, New York City, DR. MARTHA L. CLIFFORD, Hartford, Conn., and DR. HILDA H. KROEGER, Pittsburgh, Pa., were participants in a conference held by the Children's Bureau in November. Participants in this conference stressed the need to include material on the role of the doctor in adoptions in the courses directed to medical students. They agreed that doctors now in practice and the general public also need to know more about what should be expected of the doctor in adoption. Conferees developed the first draft of a statement outlining the functions that the doctor should perform. It will be reviewed by them before it is made public. Children's Bureau officials hope the final statement will be widely accepted by medical groups.

DR. RUTH S. GEIGER and Dr. J. S. Garvin addressed the 11th annual meeting of the American Academy for Cerebral Palsy, held in New Orleans in November. Their topic was "Muscular Dystrophy: Biopsy and Tissue Culture Studies."

DR. VIDA ANNETTE LATHAM, named as Medical Woman of the Year in 1956 by the Chicago Branch, AMWA, was presented a merit award on Nov. 7 by the Chicago Technical Societies Council "as partial recognition of her work in scientific and community effort."

DR. GRACE R. MARTUS, of Queens County, New York, was sworn in on Dec. 20, 1957, as medical member of the Podiatry Practice Committee of the Workmen's Compensation Board. A graduate of Adelphi College and the Boston University School of Medicine, Dr. Martus has been engaged in the practice of medicine for 27 years. She is associate physician at Queens General Hospital, associate pediatrician at the Rockaway Beach Hospital, and on the staff of St. Joseph's Hospital.

DR. MARY LOUISE NEWMAN, Jacksonville, Ill., has been elected secretary of the Illinois Obstetrical and Gynecological Society.

DR. NAN E. ROBINSON, Rome, Ga., presented a scientific paper before the annual fall meeting of the Seventh District Medical Society in Cartersville, Ga., in October.

DR. HILLA SHERIFF, Director, Division of Maternal and Child Health of the State Board of Health of South Carolina, has been elected honorary associate fellow in the American Academy of Pediatrics. This honorary classification is given to distinguished physicians, residing in The Americas, who have in some way made outstanding contributions to child health. Honorary associate fellows are exempt from fees and dues or assessments. They may serve on committees and participate in clinical sessions, but do not vote or hold office. The notification to Dr. Sheriff of her election read: "Your friends and the Executive Board wish to confer this honor upon you in recognition of your many contributions to the health and welfare of children and in appreciation of your many co-operative and understanding actions pertaining to the Academy. The Academy would indeed be most honored if you would accept this honorary associate fellowship."

DR. CAROLINE THOMAS spoke on "Familial and Epidemiologic Aspects of Coronary Disease and Hypertension" at the 14th Annual Meeting of the Association of Teachers of Preventive Medicine on Nov. 10 in Cleveland.

DR. MARGARET WATKINS, Dallas, was recently elected president of the Texas Orthopedic Association.

Book Notices

Editor's Note: These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the JOURNAL.

ANALYTICAL PATHOLOGY. Treatises in the Perspective of Biology, Chemistry, and Physics. Edited by Robert C. Mellors, M.D., Ph.D., Associate, Pathology Division, Sloan-Kettering Institute for Cancer Research; Assistant Pathologist, Memorial Center for Cancer and Allied Diseases; and Assistant Professor of Pathology, Cornell University Medical College, Sloan-Kettering Division, New York. Pp. 477, illustrated. Price $12.00. McGraw-Hill Book Company, New York, 1957.

This book contains seven chapters covering cancer, the cardiovascular system, kidney, liver, endocrine system, hematopoietic system, abnormal hemoglobins, and hypersensitivity. Dr. Mellor's introductory chapter on cancer touches on history, etiological factors of extrinsic nature (filtrable agents and virus), intrinsic factors of heredity, carcinogenic agents (dibenzanthracene), especially in animals and man, and endocrine factors in cancer etiology and therapy.

Dr. Gofman's chapter on the cardiovascular system is a logical presentation of the problem of arteriosclerosis and concentrates on the roles of blood lipoprotein levels, as related to coronary artery narrowing and hypertension.

The chapter on the kidney by Dr. Jones covers glomerular history and special histological stains, with concepts of glomerular inflammation, repair, and disease process. Etiological concepts of nephritis, nephrosis, and eclamptic glomerulonephritis, as well as vascular diseases of the glomerulus and periarteritis nodosa, are presented.

The chapter on the liver by Dr. Ratnoff presents a discussion of the cholemic syndrome and its clinical features. Relationship of hemorrhagic phenomena to disease of the liver is presented in a review of blood coagulation and the role of the liver in synthesis of clotting substances.

The chapter on the endocrine system by Dr. Russfield presents a comparison of pathological and clinical findings in man and animals, and the chapter on macrocytic anemias by Drs. Mueller and Vilter gives diagnostic methods and a modern discussion of such conditions.

The chapter on abnormal hemoglobin levels by Dr. Wiel gives a historical and practical presentation of this subject, and the chapter on hypersensitivity by Dr. Wagner presents a review of current concepts of the connective tissues of the body with an explanation of various histochemical methods of study.

An index of six and a half pages accompanies the volume, and an almost inexhaustible list of references follows each chapter. The volume encompasses a wealth of controversial and contemporary subjects that have been well outlined by the numerous authors. Advanced or graduate students and those physicians who would keep abreast of the progress of science, will be interested in this volume.

—Thomas K. Rathmell, M.D.

CURRENT THERAPY 1957. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D. Pp. 731. Price $11.00. W. B. Saunders Company, Philadelphia and London, 1957.

This ninth volume of a series started in 1949 follows pretty closely the pattern of the previous issues, whose value for quick reference is widely known. However, the present volume has incorporated 16 new articles on treatment for diseases previously not included; for instance, acquired disease of the aorta, thrombosis of deep veins of extremities, emphysema, viral dysentery, and diseases of nails. Other chapters, contained in previous volumes, have been rewritten, partly by different authors, and brought up to date in an attempt to keep pace with the swift advance in therapeutics. This applies to the articles on the treatment of peptic ulcer, diabetic coma, and pulmonary embolism with anticoagulant therapy, to name a few. For the first time, tables for normal values have been added, which facilitates matters for the reader.

—Irma Schwarzbart, M.D.

A TEXTBOOK OF GYNAECOLOGY FOR STUDENTS AND PRACTITIONERS By James Young, D.S.O., M.D., F.R.C.O.G., F.R.C.S.E., Emeritus Professor of Obstetrics and Gynaecology, University of London, and Consulting Gynaecologist, Royal Infirmary, Edinburgh, with collaborator J. C. McClure Browne, M.D., F.R.C.O.G., F.R.C.S.E., Professor of Obstetrics and Gynaecology, University of London. Tenth Edition. Pp. 523, with 297 figures. Price $9.00. The Macmillan Company, New York, 1957.

This book presents a clear, concise outline of current English teaching in gynecology. The tenth edition has been completely revised, with the addition of several new chapters and illustrations. The author submits his own approach to gynecologic diagnosis and treatment, thereby eliminating much controversial discussion and allowing for easy readability. It is a valuable addition to the library of the student in gynecology.

—Lucy A. LaSalvia, M.D.

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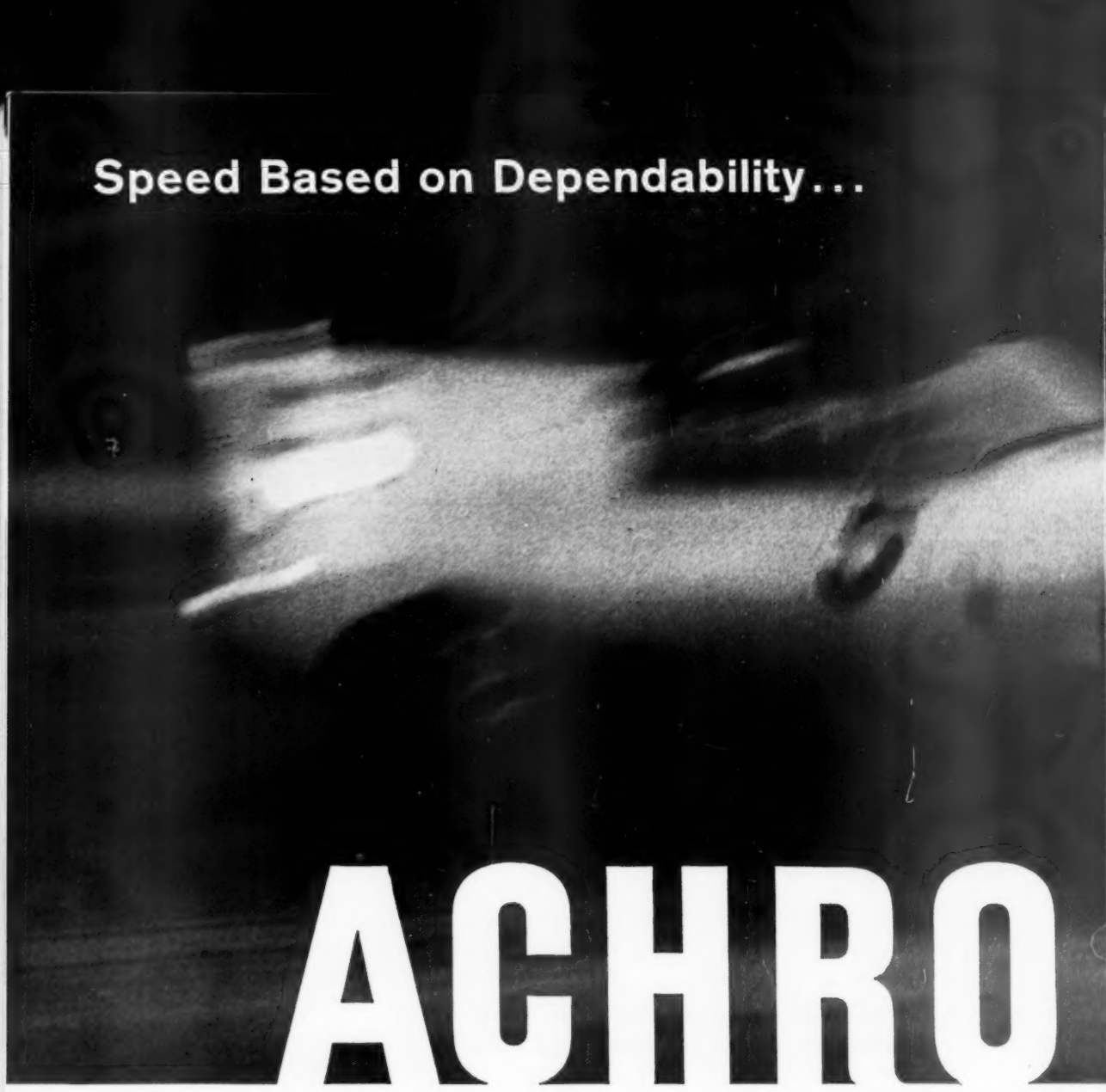

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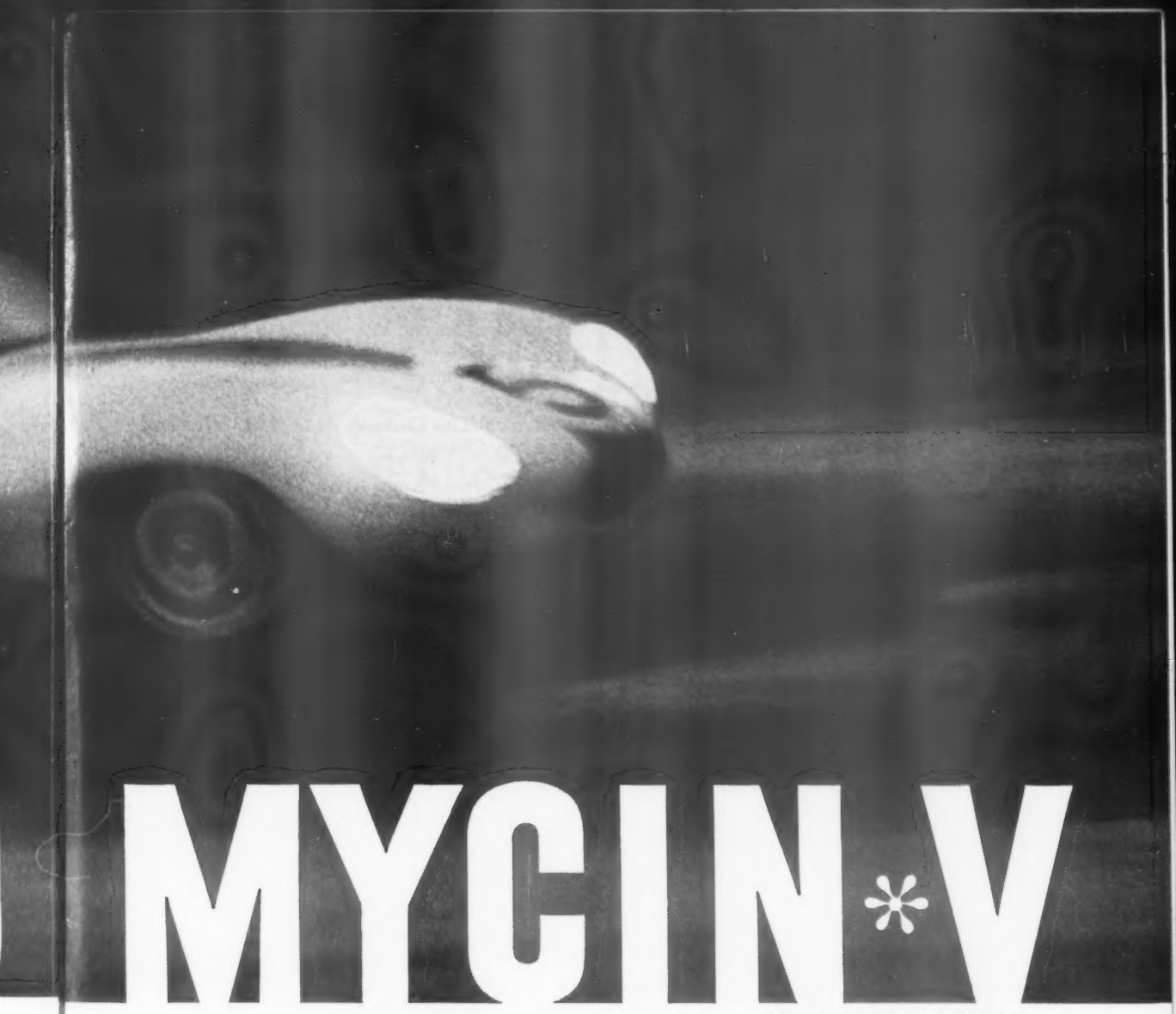

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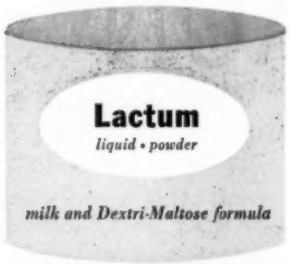

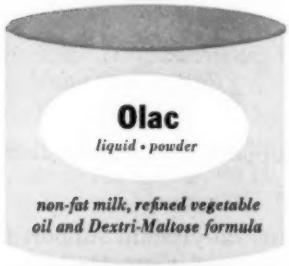

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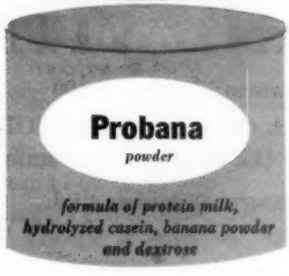

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INDEX TO ADVERTISERS

Abbott Laboratories 10-11, (16-17)
Ayerst Laboratories 22
Bristol-Myers Company 16, 19
The Coca-Cola Company 23
Eaton Laboratories 17
Lederle Laboratories 4, 30-31
Eli Lilly & Company 28
The S. E. Massengill Company .....(24-25)
Mead Johnson .....Back Cover, 34
Merck Sharp & Dohme....Inside Back Cover
Ortho Laboratories 13
Parke, Davis & Company 7
Pfizer Laboratories 35
Riker Laboratories ....Inside Front Cover, 2
Roche Laboratories .....(8-9), 27
Schering Corporation 5
G. D. Searle & Company 1, 29
Smith, Kline & French Laboratories 21
Wallace Laboratories..(36-Inside Back Cover)
Warner-Lambert Pharmaceutical Company 15, 24
White Laboratories, Inc. 8, 33
Winthrop Laboratories 20
Wyeth Laboratories 18

INDEX TO PRODUCTS ADVERTISED

ANOREXIGENIC AGENTS
Obedrin *(Massengill)* .....(24-25)
ANTACID LAXATIVES
Sal Hepatica *(Bristol-Myers)* 16, 19
ANTIASTHMATICS
Amesec *(Lilly)* 28
ANTIBIOTICS
Achromycin *(Lederle)* 30-31
Cosa-Tetracyn *(Pfizer)* 35
ANTIEMETICS
Compazine *(Smith, Kline & French)* ...21
ANTISPASMODICS
Disipal *(Riker)* 2
BABY PRODUCTS
Dextri-Maltose *(Mead Johnson)* 34
Lactum *(Mead Johnson)* 34
Nutramigen *(Mead Johnson)* 34
Olac *(Mead Johnson)* 34
Probana *(Mead Johnson)* 34
Sobee *(Mead Johnson)* 34
S-M-A Instant Powder *(Wyeth)* 18
CHILDREN'S IRON PREPARATIONS
Fer-In-Sol *(Mead Johnson)* ...Back Cover
COLD THERAPY
Romilar CF *(Roche)* 27
CONTRACEPTIVES
Preceptin *(Ortho)* 13
CORTICOID-ANTIHISTAMINE COMPOUNDS
Metreton *(Schering)* 5
DERMAL DRYING AGENTS
Selsun *(Abbott)* .....(16-17)
DIETARY SUPPLEMENTS
Redisol *(Merck Sharp & Dohme)* Inside Back Cover
Vi-Daylin *(Abbott)* 10-11
–PRENATAL
Calcisalin *(Warner-Lambert)* 15
Filibon *(Lederle)* 4
Gestatabs *(White)* 8, 33
Mol-Iron with Calcium and Vitamin D *(White)* 8, 33
Natabec Kapseals *(Parke, Davis)* 7
HEMATINICS
Iberol *(Abbott)* .....(16-17)
HORMONES
Enovid *(Searle)* 1
Milprem *(Wallace)* .....(36-Inside Back Cover)
Premarin *(Ayerst)* 22
NASAL SPRAYS
Metreton *(Schering)* 5
NEBULIZERS
Medihaler *(Riker)* .....Inside Front Cover
OPHTHALMIC SUSPENSIONS
Metreton *(Schering)* 5
SOFT DRINKS
Coca-Cola *(Coca-Cola)* 23
TRANQUILIZERS
Dartal *(Searle)* 29
Milprem *(Wallace)* .....(36-Inside Back Cover)
Miltown *(Wallace)* .....(36-Inside Back Cover)
URINARY TRACT SPECIFICS
Azo Gantrisin *(Roche)* .....(8-9)
VAGINAL THERAPEUTICS
Milibis *(Winthrop)* 20
Sterisil Vaginal Gel *(Warner-Lambert)*.24
Tricofuron *(Eaton)* 17

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DOSAGE: One tablet t.i.d. in 21-day courses with one week rest periods. Should be adjusted to individual requirements.

Samples and literature on request.

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Anxiety, tension, and related symptoms exist in most gynecologic disturbances.

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References:

1. *Pennington, V. M.: Meprobamate (Miltown) in premenstrual tension. J.A.M.A.* **164**:*638, June 8, 1957.*
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3. *Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gynec.* **9**:*703, June 1957.*

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(1) Smith, N. J., and Rosello, S.: J. Clin. Nutrition *1*:275, 1953.

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